ANTIPYRETIC AND ANTIPHLOGISTIC

METHODS OF TREATMENT

EPIDERMIC, ENDERMIC, AND HYPODERMIC

ADMINISTRATION OF MEDICINES

VON ZIEMSSEN'S

HANDBOOK

OF

GENERAL THERAPEUTICS

IN SEVEN VOLUMES—VOL. II.

ANTIPYRETIC METHODS OF TREATMENT

BY PROF. C. VON LIEBERMEISTER

ANTIPHLOGISTIC METHODS OF TREATMENT

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TRANSLATED BY

MATTHEW HAY, M.D.

PROFESSOR OF MEDICAL JURISPRUDENCE, UNIVERSITY OF ABERDEEN

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TRANSLATOR'S PREFACE.

Few names among German physicians are better known in this country than those of Liebermeister, Jürgensen, and Eulenburg; it is therefore unnecessary to introduce them to English readers. But it may be stated that they are among the highest authorities in the subjects on which they severally write in this volume.

Liebermeister's treatise deals with a subject of great therapeutical importance and present interest, and one about which all physicians are not quite of the same mind. Antipyretic treatment, and particularly the cold water form of it, has its advocates and opponents. We, in this country, have been slow to admit the value of the cold water treatment of fever. The Germans, on the other hand, became quickly convinced of its utility; and the observations and writings of no one have conduced more to this than those of Liebermeister. In his present work he has brought together the results of his extensive practical experience of antipyretic treatment, and has accompanied them with numerous observations of the precise effects of the treatment, so that we are presented with a thorough exposition of the whole subject. It seems impossible for an impartial reader to deny that his conclusions in favour of antipyretic treatment seem to be well founded. To this we, no doubt, in part owe it that the cold water treatment has been extensively tried in England within the last two or three years, and that we have at last broken our attachment to 'the old prejudices and convenient routine' with which Liebermeister

reproaches us. It so happens that quite recently—during last year—two important discussions have taken place on the cold water treatment, which enable us to ascertain the present opinion in England as to its value. The first occurred in the Medical Society of London on the reading of two papers by Dr. Coupland and Dr. Cayley. It extended over two nights, and was taken part in by several eminent London physicians; and, with one exception, all of them declared their approval of this mode of treating fever in suitable cases and with certain restrictions. The second discussion took place in the Therapeutical Section of the British Association at its meeting in Belfast, and the general opinion was again distinctly favourable to this form of treatment. Its value in the estimation of English physicians may therefore now be regarded as established. Indeed, it would appear to be proved that whereas formerly in our hospitals the mortality from typhoid fever under expectant treatment was about 16 per cent., it has now been reduced by the introduction of the cold water treatment to 9 or 10 per cent.

The works of Jürgensen and Eulenburg call for no special comments.

In translating this volume I have adhered closely to the original, in order the better to preserve the exact meaning of the authors.

Any additions which I have made are placed within brackets. At the end of the volume is a short notice which I have appended on certain new antipyretic medicines.

For the convenience of those who are not familiar with the metric system, I have, in each instance, when it appeared desirable, given the equivalent of the numbers in the English system.

I have in a separate note acknowledged my obligations to Dr. Barclay J. Baron, of Clifton, for his valuable help.

MATTHEW HAY.

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EPIDERMIC, ENDERMIC, AND HYPODERMIC ADMINISTRATION OF MEDICINES.

ANTIPYRETIC METHODS OF TREATMENT,

BY

PROFESSOR C. LIEBERMEISTER,

TÜBINGEN.

TRANSLATED BY

MATTHEW HAY, M.D.,

PROFESSOR OF MEDICAL JURISPRUDENCE, UNIVERSITY OF ABERDEEN.

NOTE BY THE TRANSLATOR.

The Translator desires to acknowledge his indebtedness to Dr. Barclay J. Baron, Physician to the General Hospital, Bristol, and formerly Assistant to Professor Greenfield, Edinburgh, for his valuable assistance in the translation of this volume. He carefully compared the translation with the original of the entire volume, and wholly translated a portion of Eulenburg's thesis, and compiled the general index.

INTRODUCTION.

It is only in recent times that antipyretic methods of treatment have come to be generally adopted in medical practice. Individual attempts, indeed, at antipyretic treatment may be traced much further back, and in part to ancient times; but it is only since the old traditional views in regard to the nature and meaning of fever underwent a complete transformation that an extensive application of this treatment and the introduction of it into practice first became possible.

From the earliest times, physicians were accustomed to look upon fever as consisting principally in an effort of nature to restore health. Their idea was that, by means of fever, the body threw off the noxious substances that had invaded it, and freed itself from the products of disease. And, though they were at the same time convinced in many individual cases that the fever by itself was fatal to the patient, yet, on account of the serious theoretical scruples which they felt, the idea of counteracting the fever by direct methods never took any firm root in their minds. It was not till after a long struggle that the faculty consented to the employment of cinchona bark in cases of ague, since the majority of the orthodox physicians apprehended from the suppression of fever the retention of the *materia peccans* and the greatest consequent dangers to the patient.

The question of the import of fever in reference to the organism will fall to be touched upon afterwards in our examination of the indications for the antipyretic treatment. In general there has of late been a decided disinclination on the

part of physicians to take up a question to appearance so purely teleological as this, and to canvas the older views on the subject; yet, on the other hand, we have gradually come to know more and more of the *dangers of fever*, and to feel more and more convinced that the cases are numerous in which patients succumb to its effects alone. It is in consequence of our knowledge of this that we have been led to look out, with more zeal than we previously did, for methods by which to counteract the fever itself and its accompanying effects, and to be able by the use of such methods to avert or remove its dangers. The perfection attained in the antipyretic methods of treatment has been in great part determined by the development of the theoretic views on the nature and dangers of fever; and even still the indications for the regulation of the antipyretic treatment must be deduced from the dangers present in each individual case.[1]

Since in every case of fever there is, *cæteris paribus*, an intensification of the process of oxidation, there must necessarily be a greater consumption of the constituent elements of the body. In most cases the process of repair cannot keep pace with the waste, since, as experience shows, during fever the appetite and the power of digestion are usually also impaired; and so there arises a *febrile waste* or exhaustion. A decided step in advance was effected in modern times in the treatment of cases of fever, when greater attention began to be paid to the waste induced by it; and it became a matter of first importance, by dietetic and other means, to lessen the oxidation of the constituents of the body, and especially to promote the repair of the parts wasted.

While febrile waste is to be particularly attended to as of

[1] In the introductory discussion of the general indications and the objects of antipyresis I presume I may be allowed to confine myself to brief notices, since I am able, as regards the proof in detail of my statements, to refer to my *Handbuch der Pathologie und Therapie des Fiebers* (Leipzig, 1875). Even when I proceed to the details of my subject I shall in many of my statements content myself with such a reference, or else reproduce individual passages unchanged, in so far as I may feel unable to improve them either in substance or form. On the other hand, when, as will often happen, a particular account of the antipyretic methods is required, a new and fuller elaboration of statement will be necessary.

special moment in chronic attacks of fever, on the other hand, in serious acute fevers, another danger emerges, in the presence of which febrile waste must be reckoned of minor importance. I refer to the danger connected with *increase of temperature.*

Every mammal, man included, quickly dies, when once the temperature of the body, whether artificially or spontaneously induced, has risen 5° or 6° C. (9° or 10·8° F.) above its normal height. If in man the temperature of the body exceeds 42° C. (107·6° F.), the most serious consequences are to be apprehended. Life cannot last long unless the temperature is quickly reduced; for if a temperature such as this lasts for any time the patient must inevitably sink under it. Now, if an increase in the temperature of the body of perhaps 5° C. (9° F.) is in all cases soon followed by death, it is natural to suppose that the rise of temperature, such as usually occurs in cases of fever, to the extent of 2°, 3°, or 4° C. (3·6° to 7·2° F.), so that the temperature amounts to 39°, 40°, or 41° C. (102·2° to 105·8° F.), will not be altogether unattended with injurious consequences; and the supposition is confirmed by actual experience. The result which rapidly ensues in consequence of an extraordinary rise in the temperature is slowly and gradually, but quite as certainly, brought about when the rise is smaller but of long duration. If the temperature of the body constantly exceeds 40° C. (104° F.), the patient will, in consequence, be sure to succumb; although in one case this will happen after a shorter, in another after a longer period, according to the patient's power of resistance.

This deleterious action of a high temperature, as anatomical examination of the bodies of those who have died in consequence proves, consists essentially in an action on the individual tissues and organs of the body, in virtue of which they readily undergo parenchymatous degeneration. This degeneration of the essential constituents of the parenchyma is to be especially remarked in the liver, the kidneys, and many other glandular organs, as well as in the heart and the voluntary muscles. It is also visible in the blood vessels, brain, &c. It is found in the human subject in all cases, without exception, in which death has resulted after a great and prolonged rise in the temperature;

and it is likewise observable in animals which have been killed by a sustained increase of the temperature artificially induced. The increase in the excretion of the urea, which appears as a consequence of any accession of temperature, whether caused by fever or by artificial means, is to be referred mainly to this parenchymatous degeneration and the accompanying decomposition of nitrogenous compounds in the system, in which the nitrogenous part is oxidised into urea and then excreted, while that which is non-nitrogenous remains behind chiefly in the form of fat.

In consequence of this parenchymatous degeneration there is, on the one hand, a diminution of the power of resistance in the tissue, so that, from causes that are prejudicial to but a comparatively small extent, serious derangements of the nutrition, or a complete breaking up of the vital powers (*decubitus* and the like), takes place ; and, on the other hand, there results a weakening of the function of the organ, or in particular cases its entire suspension.

Among the functional disturbances which appear as a consequence of a rise in the temperature not the least striking and important are those of the heart and brain, which, if they issue in paralysis in either case, necessarily cause death.

The *impairment of the function of the heart* shows itself chiefly in the increased frequency of the contractions of that organ along with a gradual decrease of power. That the increased rate of the pulse, so far as it is due to the fever, is a consequence of a rise of the temperature we conclude from, among other things, a comparison of the height of the temperature with the rate of the pulse at the same time. Such a comparison shows that the rate of the pulse is on an average higher, the higher the temperature is. It is obvious, however, in cases of fever, as well as in those in which there is no fever, that many other special circumstances may affect the frequency of the contractions of the heart ; and that, therefore, the law holds good only *cæteris paribus*, and becomes quite apparent only when the statistics of a large number of cases are examined. The excessive action of a high temperature on the heart, such as in the end issues in paralysis of that organ, shows itself especially in an unusual increase of the pulse rate, along with

great feebleness of the pulse, in combination with which there soon appear other consequences of a general weakening of the circulation: hypostases ensue; the exterior parts of the body become cold, while the temperature of the internal parts remains high; finally death results, with symptoms of œdema of the lungs. By far the majority of patients who die in consequence of fever alone, without any local disorder sufficient to cause death, die of paralysis of the heart.

Even the *disturbances of the function of the central nervous system*, as far as they are due to fever, proceed from the effects of a high temperature on the central organs. This comes out in an unbiassed comparison of the relation found to exist in the greatest possible number of cases of fever between the state of the central organs and the temperature. However different in other respects the nature of the disease may be, these disturbances completely correspond in their radical features; and their character and intensity are, irrespective of the idiosyncracy of the patient, solely dependent on the amount and duration of the rise in temperature. In cases of pneumonia, facial erysipelas, acute articular rheumatism, and traumatic peritonitis, in which the increased temperature is of equal height and equal duration, the nervous disturbances are the same as in the so called typhous diseases, or in other infectious diseases accompanied with high fever. At the same time, however, we must take this into account: that, as is obvious in certain individual cases of fever, just as in cases where there is no fever, we may in particular circumstances meet with derangements of the functions of the brain which are due to some other causes that have no, or no direct, connection with fever. It is part of an accurate diagnosis in every individual case of this nature to distinguish disturbances otherwise explicable from those due to fever. If the increased temperature continue, the disturbances due to fever issue at last in a more or less complete suspension of the functions of the brain, and paralysis of that organ leads finally to death. Pure cases of this description, and which continue so to the last, are not, however, particularly frequent; the fatal issue is due in most instances rather to paralysis of the heart. Cases of extreme prostration of the functions of the cerebrum are by no means hopeless so long as there are no symptoms of

heart paralysis. This agrees with other experiences, which likewise show that a temporary suspension of the function of the cerebrum is much less dangerous than a suspension of the function of the heart.

The more these views on the relation of the individual symptoms of fever to one another, and on the pre-eminent importance of the increase of the temperature—such as were advanced by me many years ago[1]—find acceptance, the more influence they must have in determining the theoretical principles adopted in the treatment of fever. What some of the older physicians by a fortunate presentiment conjectured, and were even able to verify more or less by direct experience, follows, according to this view, as a self-evident inference from our theoretical knowledge. As soon as we know that in numerous cases of fever the greatest danger is to be apprehended if the temperature of the body continues high for any length of time, and that in many cases the increased temperature is the direct or indirect cause of death, it follows necessarily that the essential point in the treatment is to lower the temperature of the body and keep the patient cool.

Antipyretic methods of treatment embrace all those therapeutic measures by which the temperature of the body, when increased by fever, may be lowered. Those measures are extremely varied in their nature, and may, from a theoretic point of view, as Galen[2] long ago pointed out, be divided into two groups. There are measures by the application of which a great deal of heat is abstracted from the body, and its temperature is directly lessened. These, since they are directed against the result of the fever—namely, the increased temperature—may be distinguished from antipyresis proper, and classed together as *antithermic methods.* There are other measures also by which the temperature of the body may be lowered—namely, by diminishing the production of the heat. And, strictly speaking, these are the only true *antipyretic methods.* Re-

[1] *Deutsche Klinik*, 1859, No. 40; *Deutsches Archiv für klinische Medicin*, vol. i. 1866, pp. 298, 461, 543.

[2] *Methodus medendi*, x. 10; ed. Kühn, x. p. 707 sq. See also Van Helmont, *Tractatus de Febribus*, chap. i. 18; Virchow, *Handbuch der spec. Pathologie u. Therapie*, Erlangen, 1854, vol. i. p. 43.

garded from a purely theoretical point of view, the procedures which simply abstract heat from the system cannot but seem less rational than the others, since they remove only a product of the fever, and affect only a symptom; whereas those methods, by which the production of the heat is lessened, attack, as it were, more or less the root of the mischief and are expressly directed against the source of the abnormal rise of temperature. Antipyresis proper must be regarded as the more appropriate method of the two, because by means of it the febrile waste is at the same time averted. In practice, however, so far at least as acute fevers are concerned, such a distinction is only of subordinate importance. In these cases the danger of an excessive temperature is at times so imminent, and the indication for cooling the body may be so urgent, that that treatment is to be preferred by means of which the lowering of the temperature is most certain to be accomplished; and the method by which this is effected is a matter of only secondary consideration. Neither is the distinction after all between the antithermic and the antipyretic methods to be sharply applied, since the direct lowering of the temperature of the body has an important influence on the character and the extent of the tissue metamorphosis. And, finally, it is still uncertain whether in many cases of antipyretic action the resultant lowering of the temperature arises from a diminution of the production or an increase of the loss of heat.

In the following chapters we shall speak first of the effects of the direct abstraction of heat, next of the medicines which have an antipyretic action, and finally of the dietetic treatment. In the concluding chapter we shall then be able to explain the indications for the application of antipyretic treatment and the results which the employment of it has up to the present time yielded.

CHAPTER I.

THE REDUCTION OF TEMPERATURE BY THE ABSTRACTION OF HEAT.

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HISTORICAL.

It is beyond a doubt, as we know from their writings, that the physicians of the ancient world had a distinct suspicion that there are individual cases of fever in which the patients die simply in consequence of the excessive temperature. It is easy to understand, therefore, that even at that early date attempts were made to moderate a heat so dangerous to the patient by means of some directly cooling process.[1] These attempts, however, were few and far between. No one ventured to extend them with the necessary energy to other cases, and nothing like an extensive, systematic application of the process of heat abstraction in cases of fever was ever practised in the ancient world. Even those physicians, such as Galen, who in cases of fever expressly recommended the use of cold drinks, cold spongings, and even cold baths, appear in doing so to have proceeded more upon theoretical considerations than upon practical experience.

During the Middle Ages and the first centuries of the modern era the views of both the profession and the laity were unfavourable to the application of cold water in disease. In cases of fever particularly there was the greatest dread of the internal use of cold water, and still more of its external application. The patient, on the contrary, was to be kept as warm as possible, and everything done, to the extent often of applying extra heat, to promote the presumed critical separation of the morbid matter. So recently as the second half of the seventeenth century Sydenham vigorously protested against this bad practice, and, as would seem, to a great extent in vain. At that date cold baths appear to have been something unusual even

[1] For the history of the cold water treatment reference may be made to the careful writings of Mauthner, loc. cit. pp. 119–361, as also those of Reuss, Pitschaft, Jürgensen, locis cit.

among people in good health. Yet during all this time there were not wanting individuals who recommended cold water as a remedy, in the form of draughts as well as of external applications, against the most diverse diseases ; and individuals among physicians and the laity seem to have made use of it on an extensive scale. Towards the end of the seventeenth century especially many began to look upon cold water as an important dietetic means and remedy, and to recommend the internal and external use of it to people in good health, as well as to those suffering from complaints of the most various kinds, often, indeed, in terms as if it were regarded as a sort of panacea for every possible disease and infirmity, such as phthisis and dropsy, diarrhœa and constipation, emaciation and obesity, heat and cold. The writings of that period,[1] notwithstanding all their extravagancies and their numerous critical defects, especially in regard to the considerations which might be adduced in favour of water, nevertheless had this great merit, that they lessened the dread with which cold water was regarded by physicians and the public, promoted its employment internally as well as externally among both sick and healthy, and prepared the public mind for subsequent developments. Floyer (1649–1714) was the principal advocate in England for the use of cold water ; in Germany, Siegemund Hahn[2] of Schweidnitz (1662–1742), and his two sons, Gottfried (1694–1753) and Johann Siegemund Hahn (1696–1773), employed cold water internally and externally in health as well as sickness, as also in cases of fever in the form of frequently repeated cold spongings. The work of Johann S. Hahn on the subject is the one most familiarly known.[3] It has been reproduced again and again, and had even in the present century a great influence on the development of 'hydropathy' as advocated by Priessnitz. The 'water doctors' (*Wasserärzte*) used to name him the Water Generalissimo (*Wassergeneralissimus*), and

[1] 'The true panacea is in the power and action of simple water, which not only prevents but also cures nearly every disease' (C. F. Schwertner's *Sammlung*, 6 parts, Leipzig, 1737–1743).

[2] *Psychroluposia* (sic) *vetus renovata, jam recocta*. Schweidnitz, 1738.

[3] *Unterricht von Krafft und Würckung des frischen Wassers*. Schweidnitz, 1738. Next edition, Breslau and Leipzig, 1743.

they kept issuing his work edition after edition.[1] In this production Johann Hahn appears as an intelligent practitioner who has no other cause at heart than the care and welfare of the sick; and we meet with many views in it which, though accompanied with not a few traits of credulity in regard to the healing virtues of the remedy recommended, display what at that time must be regarded as a remarkable independence of judgment. For example, he asserts, among other things, that free fresh air, so far from being, as was almost universally believed at the time, prejudicial in cases of fever, was, on the contrary, beneficial in a high degree. Besides Hahn there were other individual physicians who used in such cases heat-abstractive measures, and in the form of cold affusions; still the antithermic treatment had not up to this time attained a wide diffusion nor a methodic development.

James Currie, of Liverpool (1756–1808), is justly reckoned the real founder of the systematic cold water treatment of fever. Struck first of all with the results of the experiences of other physicians, he not only applied this treatment, and that mainly in the form of cold affusions, in numerous cases of fever, especially in typhus and scarlatina, but he sought and tried hard, by means of experiments on healthy subjects, to find out, by the use of the thermometer, the nature of the action of cold water on the human body. His method was variously followed, and for a time extensively adopted, particularly in Great Britain; the reports of the results are without exception very favourable. Even in Germany it was adopted by many physicians with good results. Among others we would refer to the reports of E. Horn, of Berlin, on the employment of cold baths and affusions in typhus, and those of A. Frölich, of Vienna, on their employment in scarlatina and other febrile diseases (loc. cit.) As late as 1821, a prize essay on the external application of cold water in fevers with a high temperature was announced in Hufeland's 'Journal der practischen Heilkunde,' in consequence of which the works of Frölich, Reuss, and Pitschaft already

[1] Edition by Oertel, third unaltered impression, Weimar, 1839; A. Erismann, *Dr. Johann Siegemund Hahn und das kalte Wasser im Jahre 1743*, Aarau, 1874.

referred to were written, to the first of which the prize was awarded.

But the impulse which Currie had given was not of lasting effect. His method gradually fell out of use, and was in the end almost forgotten. What materially contributed to this result was the circumstance that a kind of water treatment had come into vogue under the advocacy of Priessnitz, which affiliated itself in a way to the period before Currie, but less to what was excellent in it than to its excrescences and abuses. In this system there was no room for a rational treatment of fever by heat-abstractive methods; people, although they regarded cold water as a panacea for all ailments, known and unknown alike, yet seldom ventured on the cold water treatment in cases of fever; and, if they ever in exceptional cases did so, the accounts of the results are such as to show at the very first glance that they are not to be relied upon. It is not surprising that in these circumstances many a physician who had till that time indulged in the use of water in a rational way should have given up the practice in disgust. 'Nowadays,' writes Mauthner in 1836, 'body and spirit are being flooded with water; water has become a universal remedy; every creature washes, bathes—writes; one-half of literature floats in water.' And Schlechta, one of the more thoughtful defenders of hydrotherapeutics, says of the period, 'Thus arose that non-professional literature, which reached a climax between the years 1836 and 1840, whose specific aim was the removal of sundry complaints by means of the water treatment, but whose characteristic feature was an extremely unscientific, irrational mode of proceeding, an increasing laudation of water as a universal remedy, a useless accumulation of half-fallacious and falsely apprehended and half-true accounts of cases of disease, along with a perfect arsenal of abusive epithets directed against the despisers of the new method, to which class the physicians chiefly belonged.'[1] Still even this mode of proceeding was not without its good effect. It accustomed the public more than they had yet been to the idea that cold water was one of the most powerful of therapeutic agents, and so facilitated the adoption at a later date of an intelligent cold water treatment.

[1] *Prager Vierteljahrschrift*, vol. xvi. p. 78, 1847.

In the fifth and sixth decades of the century only a few physicians continued to use heat-abstractive methods in cases of fevers, such as Hallmann, Schlechta, Von Gietl, F. Niemeyer, E. Brand, and others. But the greater number of these were in the dark in regard to what properly constituted the favourable action of the hydrotherapeutic measures employed by them, since at that time determinations of temperature in cases of sickness were only gradually beginning to be again made; and, since the action of the increased temperature of fever on the organism was not known, they were far from believing that the favourable action of these measures was simply due to the cooling down of the patients. They supposed, on the contrary, and that mainly on the ground of the hydrotherapeutic theory then current, that entirely other actions were to be regarded as producing the good effect. Further, as a rule only isolated cases were subjected to the hydrotherapeutic treatment by way of experiment, or else the treatment was not conducted with that thoroughness by which alone it is possible to attain reliable results. Ernst Brand, of Stettin, is the only physician worthy of mention who applied the cold water treatment of enteric fever to any considerable extent and at the same time with the necessary methodical rigour.

The work of Brand, which was published in 1861, ranks high above the level of the publications of the professional hydropathists of that day. Still the author occupies pretty much the ground of the school of Priessnitz. The pre-eminent importance of the abstraction of heat is not sufficiently recognised; the main action of the water is much more that of stimulation. Great stress is laid upon critical discharges through the skin, particularly in the form of ecthymatous pustules, large and small boils, carbuncles, and abscesses, and in these he sees 'the most prominent and really critical symptoms in the development of typhus, and what has saved the life of many an individual.' In the practical application of the cold water treatment the author considered it unnecessary to measure the temperature. This is the more remarkable when we find that he himself in every case measured the temperature. These defects and many others are in great part to be exclusively ascribed to the time when the work appeared and to the views which still

prevailed in medical circles. And yet the work is not altogether free from prejudices that rather surprise us, and the fanaticism of subjective conviction not unfrequently takes the place of objective presentation and criticism of the facts. And this latter circumstance is, I believe, the chief consideration which explains how it happened that the experiences he communicated did not induce that conviction which was so much to have been desired. The work which appeared in 1877, and which professes to be a second edition of the first, while it exhibits a commendable endeavour after greater objectivity of statement, is still very deficient in criticism. The great merit of Brand is this, that he applied the cold water treatment with energy to numerous cases of typhus at a time when no other physician ventured to do so, and that he was the means of exciting others to the methodical investigation of the subject. It is more particularly to the stimulus communicated by him that we owe the experiments of the Kiel observer, which have opened a new era in hydrotherapeutics.

It was because in the first instance I was urged to it by the example of Niemeyer, and because in the next place, in consequence of observations I made on the injurious action of an increase in the temperature of the body, and of investigations on the immediate effect of the abstraction of heat, I became still further convinced of the suitability of the method, that ever since the year 1859, in all serious cases of enteric fever that have come under my treatment, in which there did not happen to be special contra-indications, I have myself regularly adopted temperature-reducing measures, such as cold affusions, cold packs, and cold baths. The results obtained from many hundreds of cases prior to 1866 must, as compared with those under the ordinary treatment, be characterised as decidedly favourable; but they were up to that time not satisfactory. For the object, which was to remove the danger of the increase of the temperature by applications that would lower the temperature, was only partially attained. Till the appearance of the work of Jürgensen I ventured as a rule to recommend baths only once a day, and it was with no small hesitation that I occasionally prescribed more frequent recourse to them.

The observations of Bartels and Jürgensen, which enabled

me to overcome my hesitation, and of which a detailed account is given in the work of the latter in 1866, inaugurated a new epoch in the history of the treatment of fever. It was demonstrated in an objective and strictly scientific way that more than ordinarily favourable results were reached by means of heat-abstractive processes, provided they were of the requisite intensity, and, especially, if employed with the requisite frequency; and it was shown, moreover, that under such treatment, though frequently repeated, the patient suffered no inconvenience. Since then the method employed at Kiel has, with immaterial variations at times, been adopted in many other hospitals, and, where conducted with the necessary rigour, it has always been followed by extraordinarily favourable results. This has been the case particularly in Barmen, Bremen, Basel, Dresden, Erlangen, St. Gallen, Greifswald, Halle, Heidelberg, Jena, Leipzig, Munich, Nuremberg, Prague, Vienna, Würzburg, Zürich, and other places. Both on the battle-field and in military hospitals numerous physicians have put the method to the test, and found it satisfactory. It has become already so completely naturalised in private practice in many localities that the public anticipates the employment of heat-abstractive process in severe cases of fever as a matter of course. Even in France, since the late war, the cold water treatment has begun to take root. In England, on the contrary, the native land of Currie, the majority of physicians appear still to cling so firmly to their old prejudices and the convenient routine which has prevailed hitherto that they have not been able for once to resolve to give this treatment a trial.

The Theory of the Reduction of Temperature.

The nature and manner of the action of heat-abstractive processes in cases of fever may, perhaps, at first sight appear very simple. Everyone knows that in order to cool down a body that is too hot, the simplest thing to do is to plunge it into cold water. If, therefore, we believe that the real danger in fever is the too high temperature of the body, it seems self-evident that the cold water treatment is the simplest and the most appropriate method of treatment.

But if the matter were actually as simple as it was at one time almost universally believed to be, and as individuals perhaps still fancy, it would be plainly incomprehensible how it happened that the cold water treatment of fever, which was occasionally resorted to even by the physicians of a by-gone age, should ever have fallen into disuse, and that the universal adoption of it in our time should still here and there encounter opposition.

The living human body behaves differently under an attempt to artificially cool it than would a mass of matter without life. A man in health possesses the capability of *regulating the heat* of his body, and of maintaining its temperature steadily, in spite of changes, at a definite height. This adjustment of the temperature is managed on the one hand by *regulating the loss of heat.* If the external physical conditions render the giving off of heat difficult—as, for instance, under a relatively high temperature of the surrounding air—the result we witness is a relaxation of the skin and a dilatation of the cutaneous vessels, so that the greatest possible quantity of blood is transferred from the interior to the surface of the body, where it is exposed to the cold; and, as a further result, there is an increase of the transpiration and the sweat secretion, and in consequence of this an increase of the loss of heat by evaporation. The reverse is the case if external circumstances raise the quantity of heat evolved above the usual amount, as, for instance, in a relatively cold atmosphere; in that case the skin contracts, and also the vessels at the periphery—the skin becomes dry; the heat given off is not so great as it would be were the external circumstances different. The loss of heat is likewise regulated according to the production. If, for instance, under bodily exertion the production of heat is considerably in excess of the usual quantity, the superfluous amount is got rid of as quickly as possible through the cutaneous apparatus.

But the regulation of the loss of heat would be insufficient to maintain an approximately constant temperature of the body. There are circumstances in which, notwithstanding all regulative arrangements, the loss of heat is considerably above the usual quantity; such is the case especially in the cold bath, or under other powerful heat-abstractive appliances. But even in that

case the body is able for a certain time to maintain a strong internal temperature, and that by the production of the heat being increased equally with the increase of the loss. Thus there comes to be *a regulating of the production of heat in proportion to the loss of it.*

This is not the place to enter upon a minute discussion of this subject, which is, however, of fundamental importance for understanding the nature of fevers. For a detailed account of it I may refer to the second section of my 'Handbuch der Pathologie und Therapie de Fiebers,' to which account in all particulars I still adhere. Only I may add to the statements there made, that this important section of pathology, with which, for a long time back, pathologists have been considerably occupied, has at length received in the hands also of the physiologists a more thorough investigation; and that, at the present time also, besides the researches conducted some time ago in Ludwig's laboratory, the results which the investigations of Pflüger and his pupils,[1] as also those of Voit and his followers,[2] have yielded, furnish a complete confirmation of the views I have submitted above, and constitute a broader basis of great value in support of our theory of fever. The much-debated question as to the existence of a control of the production of heat may be therefore accepted as finally settled. Pflüger,[3] at least, is of opinion that the 'control of the bodily temperature of warm-blooded animals, by regulating the production and the loss of the caloric,' will be no longer questioned by any physiologist.

What applies to a healthy man in this respect applies also to a patient suffering from fever. The latter may control the temperature of the body by regulating the production and the loss of heat, and so keep it relatively constant. Only he does not regulate it with reference to the normal temperature of about 37° C. (98·6° F.), but with reference to the higher temperature corresponding to the temporary degree of the fever. Even in the case of fever patients, when a process of heat abstraction is commenced, a lowering of the internal temperature

[1] *Pflüger's Archiv für Physiologie*, vol. xii. et seq.
[2] *Zeitschrift für Biologie*, vol. xiv. 1878.
[3] *Archiv für Physiologie*, vol. xviii. 1878, p. 321.

does not immediately take place; under certain circumstances, exactly as in the case of a healthy subject, we observe at first a trifling rise rather; the processes of oxidation become more active in proportion, so that in spite of the increased loss of heat the temperature of the body is kept constant.

It is in this regulating of the production of heat according to its loss, which takes place in fever just as in health, that the real obstacle to the lowering of the temperature of the patient lies. The question arises: Can this obstruction be overcome? We have been taught long ago by experience that it is possible, but at the same time that mild measures are not enough to secure it.

If the process of heat abstraction is very active, if, for instance, during a certain space of time, six times the quantity of heat is withdrawn from the body that it would lose in the same time in ordinary circumstances, the regulation of the production of heat becomes after a while inadequate, and the temperature of the body begins actually to fall. Thus, in health, the regulation of the body heat may be overcome by an excessive abstraction of it; and it is exactly so in fever: perhaps with this distinction, that in fever the means for the regulation are not quite so effective as in health, and hence the resistance to the cooling is on the whole somewhat less energetic. Yet even in fever it is only when the heat-abstractive process is powerful that any remarkable effect is to be noticed on the temperature of the body.

One other circumstance contributes to the possible cooling of the body. Observation shows that when a large abstraction of heat has taken effect, there is a secondary and additional lowering of the temperature of the body, occurring subsequent to the immediate effect of the heat abstraction. This secondary action is accounted for, at least in part, by this, that, owing to the abstraction of the heat, even when the temperature of the internal parts of the body was at first either not at all or only slightly lowered, that of the external parts was considerably reduced; and that now, after the cessation of the primary effect of the heat abstraction ceases, an equalisation of the temperature takes place between the different regions of the body. Hence it happens that, after an intense abstraction of heat,

the lowest internal temperature is not as a rule observed immediately after the operation, but from half an hour to an hour afterwards, or even still later.

We therefore perceive that, although the human organism offers an energetic resistance to any lowering of its temperature, yet it is possible to effect a reduction of temperature, by means of forcible control over the regulation of the heat on the one hand, and in virtue of the secondary action on the other hand. But if this mode of treatment is to succeed in the case of a patient suffering from fever in any degree obstinate, vigorous measures are necessary to lower the temperature of the interior by 1° or 2° C. (2° to 4° F.)

Even still it sometimes happens that a physician commences the cold water treatment with high hopes, but finds himself deceived in his expectations, because he supposed he could reach his object by easy means, i.e. by gentle or moderate abstraction of heat. Then sometimes, after observation of some mild cases, the announcement is made that tepid baths, or simple cold spongings, or a few ice bags are quite sufficient and quite as effective as thoroughly cold baths; and if, thereafter, the first serious cases come for treatment, then the second announcement follows, in which it is affirmed on the ground of experience that the cold water treatment yields no better results than the expectant treatment. Certain physicians have even brought it so far as to be able to make both communications at one and the same time.

There is still one other misapprehension to be disposed of, if we would guard against disappointments in the cold water treatment of fever. In former times observers usually made experiments with this treatment on the assumption that, if only the temperature were lowered and the fever interrupted, this must have a lasting effect through the whole course of the disease, or at any rate for a considerable period. For years I deemed one vigorous abstraction of heat per diem enough; and although I knew that by that means the end contemplated was not reached, I but seldom ventured to go further, because I thought that I had to be on my guard against injury to the patient from too frequent employment of such an heroic measure. In reality the temperature, whenever it has been lowered by one

great withdrawal of heat, usually soon rises again, and in other respects the condition of the patient, which usually shows signs of apparent improvement after the operation, soon becomes worse again. In general, a rising in the temperature again follows, and the more quickly does the temperature rise the severer the case is, and the more obstinate the fever ; so that it is just in those cases in which the necessity for heat abstraction is most strongly indicated, that its effect is of the shortest duration. Now Currie, in fact, taught us long ago that the cold bath must be as often repeated as the returning rise of the temperature necessitates : that it is sometimes necessary to employ it 10, even 12, times in the 24 hours (loc. cit. vol. ii. p. 53) ; that he had employed affusions among other cases even on his own children, who were suffering from severe scarlatina, in the case of one of them 14 times, and in the case of the other 12 times during 32 hours (loc. cit. p. 63); but these experiments did not receive the attention they deserved. Not till the observations at Kiel were published by Jürgensen (loc. cit.) did we feel satisfied that baths really cold might be used without any risk for most patients, as often as they were necessary, i.e. as often as the internal temperature rose again above a certain limit. It has everywhere been proved that the great results of the cold water treatment are reached only by *a steady control of the temperature of the patient, and by the application of effective heat-abstractive measures as often as may be necessary to attain the desired object.* In what form in individual cases the indications for the abstraction of heat are presented, and from what special point of view the sphere and aim of the cold water treatment are to be formulated, will be examined in detail further on (Chap. IV.)

Methods Employed for Reducing Temperature, and the Extent of their Action.

There is a great variety of methods by means of which the temperature of fever patients may be reduced. For this purpose there have been employed cold affusions, douche and spray, cool and cold full baths, half-baths, sitz baths, cold packings, cold spongings, cushions containing cold water, or ice or cold

mixtures, on which the patient is laid; local reduction of temperature by means of cold compresses or applications of ice; internal reduction by cold drinks, by swallowing ice, or by the injection of cold clysters. In former times physicians who employed one or other of these methods used to calculate upon particular specific results from the method adopted, which they did not believe could be expected from the others. And it is certainly not to be denied that all these methods, whilst contributing to the reduction of the temperature, do affect the organism in many other ways besides, and that these other effects vary to some extent with each method. We do not, however, need in the first instance to pay any regard to these diversities, since all these processes are introduced here only in so far as they belong to the antipyretic methods of treatment, and in our own day there can be no doubt whatever that the antipyretic action of all of them depends essentially on their power to abstract heat.

The question as to which of these different methods deserves the preference does not admit of an answer in any positive terms. We are left at perfect liberty rather to choose and apply whichever seems best in the circumstances. Such circumstances may in part be quite extraneous, such as, for instance, the wishes and prejudices of the patient and those about him, the hospital arrangements at our disposal, and, in private practice, the presence or absence of one or another means of help; and they are in part dependent also on the idiosyncrasy and the immediate condition of the patient. We should always, of two equally effective methods, choose the one which in a given case is attended with the fewest difficulties and inconveniences.

In order to make such a selection, however, as will be suitable in the circumstances, it is necessary to have at least an approximate conception of the effect of the action of each method. Our knowledge as respects this is as yet very imperfect, but we possess at least some positive data to guide us, expressible in numbers which are not altogether valueless, and that in a province in which hitherto only conjecture and more or less arbitrary estimations have been possible.

In order to rightly estimate the action of a particular heat-abstractive process, or to compare the effects of different methods,

we must first of all have a standard by which to measure the amount of the action. Since the purpose of the abstraction of heat is the lowering of the temperature of the body, we must in general pronounce that heat-abstractive process to be the most effective by which the temperature of the body is most reduced. But now it seems that under the same process the resultant lowering of the temperature may vary very considerably, and that not only in different individuals, but even in the same individual at different times.

This diversity of effect was remarked by the first observers who made regular determinations of temperature (e.g. Brand, loc. cit. 1861, p. 105). We are able to specify many of the circumstances on which this diversity depends, and shall, further on, have to speak in detail of some of those which are of special practical importance. We must, for instance, take into account the volume of the body, the relation of this to the superficial area of it, the thickness, too, of the subcutaneous fatty tissue, the activity of the circulation, and many other individual circumstances. But even in the same individual the temperature of the body behaves itself very differently after an equal abstraction of heat at different times; and indeed the state for the time of the production of the heat and its regulation has often a more important influence on the extent of the reduction of the temperature than the quantity of the heat withdrawn. If, for instance, the heat is withdrawn at a time when the temperature is of itself on the point of falling, the decrease of the temperature may be unduly large; but if, on the other hand, it has a tendency to rise at the time when the heat is being withdrawn, the effect may, measured by this standard, even after a very thorough abstraction of the heat, appear entirely null or even negative. Moreover, according to the time, either during or after the withdrawal of heat, selected for the observation of the effect, and according to the locality in which the determination of the temperature is made, the effect may, in the same case, appear great or small, and even positive at one time and negative at another. Finally, in particular cases, it is possible to obtain some notion of the severity of the fever, especially as regards its obstinacy; and, under certain circumstances, the effect of the heat abstraction on the temperature of the body may so

far be of prognostic value, as from it a conclusion may be arrived at in regard to the future gravity of the case, and what course the fever may be expected to take. The degree of the reduction of temperature effected by the withdrawal of heat is thus the result of a great number of factors whose relations to one another are much too complicated to warrant us to hope that we may be able to find in the gross result a sure measure of the amount of the action of any single one of them. Such a measure of the amount of the action due to each method is to be obtained from the condition of the temperature of the body, only when the number of the observations is large enough to admit of an estimate in a statistic form, when it may therefore be assumed that in the resulting averages the difference produced by the action of every other factor can be approximately eliminated. In fact the statistic method has been already applied with success in the determination of the effect of heat abstraction (see Ziemssen and Immermann, loc. cit.)

The results are independent of other influences, and therefore more readily comparable, if in the first series we have regard only to the amount of heat which has been withdrawn from the body under the different methods. In many cases the amount of heat which the water withdraws from the body can be estimated in a very simple way. Thus, in the application of the cold bath, it is only necessary to know the quantity of water used in the bath, and to observe how much its temperature rises during the time of the bath. If the quantity of water is expressed in kilogrammes, and the rise in the temperature in degrees Centigrade, then the product of the quantity of the water and the rise in the temperature yields directly the quantity of caloric, or units of heat, which the water has withdrawn from the body. In many other forms of heat abstraction the method is somewhat more complex.

In regard to the details of the method of experimenting, and the necessary corrections, as well as some further deductions, I must refer my readers to my earlier publications (loc. cit.)

In what follows I designate *the quantity of heat or caloric, which is withdrawn from the body by a heat-abstractive process, as its 'extent of action'* ('*Wirkungsgrösse*').

Further, the *lowering of the temperature of the body*, which

is effected on an average by the withdrawal of heat, will be also taken into account in the determination of the extent of action of a heat-abstractive process.

Full Baths.

The most effective method, and the one most commonly adopted in recent times, of withdrawing heat, consists in the use of the cold bath. The abstraction of heat effected by this means is in general larger, the lower the temperature of the water in the bath is, and the longer the patient remains in it.

An approximate idea of how much the extent of the action of the bath is dependent on its temperature and its duration is given in the following table, in which, according to observations made on four fever patients, there is tabulated the quantity of caloric which was abstracted from the body of each patient by baths of different temperature, after 5, 10, 15, &c., minutes. The first of the patients mentioned was suffering from acute croupous pneumonia, the rest from enteric fever.

I. *Table showing the Extent of Action ('Wirkungsgrösse') of the Cold Bath on Fever Patients.*

Average Temperature of Bath		Name of Patient	Weight of Patient in Kilgr.	Duration of Bath	Temperature in the Rectum				Reduction of Temperature		Amount of Heat[1] abstracted by the Water after						
					before the Bath		after the Bath				5′	10′	15′	20′	30′	45′	60′
°F.	°C.			′	°F.	°C.	°F.	°C.	°F.	°C.							
68·0	20·0	Henzler	75·2	31	105·3	40·7	102·4	39·1	2·9	1·6	151	220	274	316	397	—	—
82·6	28·1	,,	,,	46	104·2	40·1	103·8	39·9	0·4	0·2	54	85	111	132	174	232	—
70·7	21·5	Dieter	55·0	30	104·2	40·1	101·7	38·7	2·5	1·4	100	150	195	231	297	—	—
89·6	31·8	,,	,,	63	104·4	40·2	104·0	40·0	0·4	0·2	23	44	55	70	95	132	169
73·4	23·0	Hodel	39·0	18¾	104·7	40·4	101·0	38·3	3·7	2·1	68	103	138	167	—	—	—
85·3	29·6	,,	,,	29¾	,,	40·4	102·6	39·2	2·1	1·2	49	76	97	114	151	—	—
93·7	34·3	,,	38·5	43½	104·7	40·5	103·5	39·7	1·4	0·8	15	27	37	43	65	94	—
94·1	34·5	,,	,,	44½	105·3	40·7	,,	39·7	1·8	1·0	11	23	32	40	63	99	—
75·4	24·1	Beitter	61·0	32	105·6	40·9	105·1	40·6	0·5	0·3	79	115	147	170	215	—	—
90·1	32·3	,,	,,	49	104·4	40·2	104·8	40·4	0·4	−0·2	12	22	34	44	68	100	—

[1] Amount of increase of temperature in degrees C. multiplied by the amount of water in kilogrammes.

The comparison of the quantities of heat given off in baths of different temperatures by the separate persons experimented on, shows to what a great degree the extent of action of the baths is dependent on their temperature. Thus, for instance, the extent of action of the bath of 28·1° C. in the case of the first patient is in the same period of time not half so great as that of the bath of 20° C.; in the case of the second patient, the heat withdrawn by the bath of 31·8° C. is less than a third of that withdrawn by the bath of 21·5° C., &c.

From this it follows that *baths must necessarily be of a low temperature if they are to act powerfully in withdrawing heat.* If an effective heat abstraction is indicated in the case of an adult, the temperature of the bath must in no case be higher than 20° C. (68° F.) As a rule, it should be reduced still lower, as far as 15° C. (59° F.)

It is further evident from this table that the greatest abstraction of heat in cold baths occurs during the first few minutes in the bath, while afterwards it is considerably less. Thus, for instance, in the case of the first patient, the quantity of heat which was given up to the water in the bath of 20° C. amounts for the first ten minutes to much more than the double of that which is given up every ten minutes after. In the first five minutes it is considerably greater than during ten minutes afterwards; and so is it similarly in the other cases in the cold baths.

These facts are easily explained. At the commencement of the bath, the surface of the body, where naturally the heat abstraction first occurs, possesses a high temperature and must part with much of its heat. In the further course of the bath, the surface is already cooled, and therefore it gives off less heat. From this we infer that *it is not desirablè to keep the patient too long in the bath; much more is gained if baths of short duration are frequently repeated.* In fact, two cold baths, of 10 minutes' duration each, effect much more than a single bath of 20 minutes. And in this we must also take into account that, as experience shows, the patient is less exhausted by a succession of baths of short duration than by a single one unduly prolonged. The cold bath should, as a rule, not exceed 10 minutes. If we wish to increase its action, this is more cer-

tainly secured by lowering its temperature than by prolonging its duration. And *vice versa*, if we wish to lessen the shock in the case of a patient for whom a bath of 15° C. (59° F.) seems too strong, the action of the bath is less injurious if we reduce the duration of it than if we use a higher temperature.

From what we have so far adduced, it follows that we are correct only to a very limited extent, if we think that we can by means of tepid baths—if we only allow the patient to remain in them for a longer time—accomplish the same effect as by means of cold baths. The extent of the action of a bath decreases with a higher temperature of the water so quickly that the action of a tepid bath as yet can scarcely be compared with that of a cold one. Only in the case of little children, in whom the surface of the body is very large as compared with the volume of it, can an adequate lowering of the temperature of the body ever be reached by means of moderately cold baths. In other respects, children are affected by the abstraction of heat in the same manner as adults; they bear it equally well; and, guided by the same indications for its need, we need not hesitate to resort to its employment.

The distinction between the extent of action of cold and of tepid baths becomes especially clear if, besides the amount of the heat abstraction, we take account also of the time that is necessary to effect this. A certain amount of heat is evolved by the patient in ordinary circumstances when he lies in bed, and the action of the cold bath depends essentially on this, that the quantity of heat evolved is raised above that which normally takes place. I call that quantity of heat the 'net effect' (*Nutzeffect*) of the cold bath, by which the quantity of heat abstracted by the bath exceeds that which is normally evolved by the body. The number for the net effect is obtained if we deduct from the heat actually found to be given off during the baths that which would have been given off without the bath in the same time. In the following table the approximate value of the net effect for the above-mentioned experiments is given. It appears still more clearly from this table how much the action of the colder exceeds that of the warmer bath, and that even a long-continued tepid bath cannot have the same effect as a cold bath of short duration.

II. *Table showing the Net Effect ('Nutzeffect') of the Cold Bath on Fever Patients.*

Average Temperature of Bath		Name of Patient	Weight of Patient in Kgr.	Net Effect of the Bath after a duration of						
° F.	° C.			5′	10′	15′	20′	30′	45′	60′
68·0	20·0	Henzler	75·2	139	198	242	274	333	—	—
82·6	28·1	,,	,,	44	66	83	96	123	156	—
70·7	21·5	Dieter	55·0	93	135	173	202	253	—	—
89·3	31·8	,,	,,	16	29	33	41	51	67	82
73·4	23·0	Hodel	39·0	62	91	121	144	—	—	—
85·3	29·6	,,	,,	43	64	80	91	117	—	—
93·7	34·3	,,	38·5	9	15	20	20	31	43	—
94·1	34·5	,,	,,	5	11	15	17	29	48	—
75·4	24·1	Beitter	61·1	71	99	124	139	168	—	—
90·1	32·3	,,	,,	4	6	11	13	21	30	—

The lowering of the temperature of the body effected by baths of different temperature and duration corresponds, as to its extent (as the numbers in Table I. show) in general, with the conclusions deduced from the observation of the abstraction of heat. It is distinctly greater in the cold bath than in the tepid bath. It is evident also that a lower temperature of the bath cannot be compensated for by a longer duration of the bath.

Baths Gradually Cooled.

In many cases it is desirable to employ baths whose temperature is somewhat higher at the beginning, and is afterwards gradually cooled down to the desired extent. Ziemssen, who was the first to recommend the gradually cooled bath,[1] describes the process in this way: 'The patient is put into a bath the temperature of which is about 5° to 6° C. (9° to 10° F.) below that of his body, and, consequently, in the case of a bodily temperature of from 40° to 41° C. (104° to 106° F.), it amounts, perhaps, to 35° C. (95° F.) Into the bath, whilst two assistants keep rubbing the skin of the trunk and the extremities (quite gently, however) with the palm of the hand, there is poured,

[1] *Centralblatt für die med. Wissenschaften*, 1866, No. 41.

gradually and intermittently, tolerably cold water, which is best done by means of a tube opening deep under the surface of the water, until the temperature of the bath is, after from 10 to 15 minutes, lowered to about 20° C. (68° F.) A lower temperature is seldom necessary. On the whole, the patient remains from about 20 to 30 minutes in the bath, that is, till, in spite of the rubbing, and in spite of the friction of the water, severe shivering or chattering of the teeth begins. Then the patient must be quickly removed into a bed previously warmed, and be well covered' (Ziemssen and Immermann, loc. cit. 1870, p. 2).

These baths are more agreeable to many patients than those that are cold from the first. The somewhat greater trouble connected with them interferes with their introduction into practice. Yet this objection is in private practice easily overcome, if there is only one patient to be treated, and sufficient help can be got. And even in large hospitals, with numerous fever patients to be treated at the same time, the process, provided the water arrangements are suitable, is not too difficult to carry out. Finally, there are cases in which this mode of heat abstraction is the only one applicable—for instance, where a certain degree of feebleness of the heart exists, and where, perhaps, there co-exist a low temperature of the periphery and a higher temperature of the interior of the body. Should we have recourse in such cases to heat abstraction, it can be effectually accomplished, and at the same time without risk, if the patient is placed in a warm bath, and then, only after some time has elapsed, subjected to gradual cooling. Further, these baths are to be recommended in the case of all individuals who are much enfeebled, and for those who are sensitive, or afraid of cold water.

The extent of action of a gradually cooled bath does not readily admit of being determined calorimetrically; yet it is probable that Ziemssen's estimate—that the effect of such a bath of 30 minutes' duration is perhaps quite as considerable as that of a bath, cold from the commencement, of 10 minutes' duration—pretty nearly corresponds to the actual fact. With this result also agree the observations made on the decrease of the temperature of the body after such baths. This decrease,

according to Ziemssen and Immermann (loc. cit. p. 100), amounts, on the average, in a great number of observations, from 1·9° to 2·4° C. (3·4° to 4·3° F.), according to the period of the day; this excludes the serious cases, whose daily variations were less than normal, and in which the fever was often of particular obstinacy. In any case, if the cooling down is only carried far enough, an effect as complete as that of an ordinary thoroughly cold bath can always be secured.

The Cold Affusion.

In cases of fever Currie employed cold affusions, in preference to every other method, for the purpose of reducing the temperature, and this method was that usually adopted by his followers. Bartels and Jürgensen also at first employed affusions in the form of the spray douche, and only had recourse to cold baths at a later date. Since then baths have come more and more into use, and affusions are less and less frequently resorted to.

In 1859 and 1860 I instituted experiments to determine the extent of the action of cold affusions. In these the temperature of the water employed was accurately determined both before and after the experiment, and the quantity of the heat abstracted from the body by the water was by that means ascertained. In the following table I give only the results, and I refer for the details to my previous account of the experiments (loc. cit. 1868, p. 150 et seq.)

	Approximate Weight of Patient	Temperature of Water		Duration of Affusion	Quantity of Water	Heat abstracted	Temperature in the Axilla				Decrease of Temperature	
							before		after			
		° F.	° C.	Mins.	Ltrs.		° F.	° C.	° F.	° C.	° F.	° C.
Healthy person . .	61	71·4	21·9	4	40	35	99·3	37·4	99·0	37·2	0·3	0·2
Typhus patient I. .	40	63·0	17·2	2–3	(14)	25	101·3	40·2	103·6	39·8	0·7	0·4
Typhus patient II.	40	73·9	23·3	10	38	62	104·3	40·2	102·9	39·4	1·4	0·8
" "	"	71·1	21·7	5¼	46	76	103·3	39·9	101·4	38·6	2·4	1·3
" "	"	74·5	23·6	5	56	52	103·5	39·75	101·1	38·4	2·4	1·35
Typhus patient III.	80	72·1	22·3	?	56	90	104·9	40·5	103·8	39·9	1·1	0·6
" "	"	74·8	23·8	5	36	54	105·4	40·8	104·9	40·5	0·5	0·3
" "	"	73·2	22·9	7	46	63	104·9	40·5	104·0	40·05	0·9	0·45
" "	"	63·4	17·4	?	60	74	104·0	40·0	104·2	40·1	0·2	– 0·1
" "	"	73·7	23·2	6¾	70	79	105·3	40·7	105·1	40·6	0·2	0·1
" "	"	70·7	21·5	7½	92	94	105·4	40·8	104·0	40·0	1·4	0·8

The temperature of the body was estimated in the axilla, and the lowest reliable estimation of the temperature after the affusion was that which was recorded. The amount of the water used for the affusion is given in litres, the weight of the body in kilogrammes.

If we compare these results with those which were obtained by means of cold baths, it will appear that *cold affusions are much less effective in reducing the heat of the body than full baths of like temperature and duration.*

This result does not altogether correspond with prevailing ideas. We are accustomed to regard the cold affusion, since of all heat-abstractive methods it produces the greatest shock, as being also the most effective. And I myself shared in this opinion up to the close of these investigations. Closer reflection, indeed, must have led *a priori* to another result; for, in the case of the affusion, the contact of the surface of the body with the heat-abstracting medium is less complete and constant than in a bath.

In order, however, to estimate the value of the affusion many other considerations must be taken into account. In all circumstances a cold affusion creates the impression of being a heroic remedy. To the patient's friends it seems a severe measure, justified solely by the conviction of its absolute necessity as enforced by the authority of the physician. To the patient it is in the highest degree unpleasant; if he has not perfect control of himself he struggles often violently, or even screams aloud. Indeed, intelligent adult patients, when they really felt better after the affusion, have often confessed, in answer to my inquiry, that they would willingly submit again to this treatment if it were absolutely necessary, but at the same time stated that it was exceedingly uncomfortable. A bath, on the other hand, of similar temperature and duration is less disagreeable; and all patients, I am persuaded, if left to their own choice, would much rather consent to a frequent repetition of baths than affusions. In fine, if we further reflect that the cold bath may be prolonged for 10 minutes without any great uneasiness, while for the affusions 5 minutes' duration is quite long enough, it is clear that, as regards the heat-abstracting effect, the affusions accomplish much less than the baths,

and at the same time the discomfort is considerably greater. It must be admitted, however, that if the affusion is made with a large, continuous stream of water, by means, for instance, of a cold spray douche, its extent of action will approximate somewhat more to that of a bath of similar temperature and duration.

Ziemssen and Immermann, who employed a cold affusion of from 10 to 15 minutes' duration in a shallow bath of 29° C. (84° F.), with water of from 10° to 15° C. (50° to 59° F.), accompanied by constant gentle friction of the skin, found the action on the temperature of the body considerably less than that of a gradually cooled bath (loc. cit. p. 113 et seq.)

Since, by means of the calculations and comparisons referred to, I came to know that the heat-abstractive action of the affusion is materially less than that of the cold bath, I have ceased to employ it for the purpose of heat abstraction.

On the other hand, the cold affusion is an indispensable means for meeting another indication, viz. when it is wanted to vigorously stimulate defective respiration, or failing psychical functions due to paralysis; then cold affusions are to be recommended. In cases of fever with the temperature of the body continuously high, if there is a great tendency to deep sleep or to coma, or if even furious delirium exists, provided there are no signs of commencing paralysis of the heart, cold affusions in an empty tub, or in a tepid half-bath, are of special service. The more, under these circumstances, symptoms at the same time appear which point to the possibility of a sudden collapse from feebleness of the heart, the more is it advisable to keep the greater part of the body immersed in tepid water during the affusion. Finally, in cases in which no stress is laid on the accompanying heat abstraction, I would recommend the cold affusion in a warm bath; as, for instance, if, on the abatement of the fever, serious symptoms of cerebral paralysis continue; further, in certain conditions of cerebral affections, and in numerous forms of imperfect breathing due to various causes; in particular, also, in cases of poisoning with carbon monoxide, and in many other forms of poisoning. If it is wished only to act on the head, the patient must remain at the time of the affusion immersed in warm water nearly up to the neck.

If, on the other hand, stimulation of the respiration is at the same time, or chiefly, indicated, the patient, in order to receive the benefit of the affusion, is raised with the greater portion of the upper part of the body above the surface of the water, and, immediately after the affusion, is plunged again into the warm water up to the neck. Except the faradisation of the phrenic nerves, I know no means of stimulating the respiration so effectively. Where, for instance in serious cases of poisoning with carbon monoxide, it is necessary to employ such an operation for a longer time, the temperature of the bath must be kept up, at perhaps 35° C. (95° F.), by repeatedly drawing off a portion of the water in the bath, and pouring in warm water. This is quite practicable even in private practice. Thus, for example, in a very severe case of poisoning with morphia—that of a student of medicine—after previous faradisation of the phrenic nerves I continued, as described, the affusions in the warm bath for more than 6 hours. The patient remained all this time in the bath, and, as often as the very slow respiration became insufficient, had his head, breast, and back drenched, about every 10 or 15 minutes, with two or three litres of cold water; the effect every time was surprising. The case terminated favourably.

The Cold Pack.

A method of heat abstraction which, urged to it chiefly by my superior at that time, Professor Niemeyer, I in former years frequently employed in preference to every other, and which recommends itself particularly because it is attended with only very slight discomfort to the patient, consists in cold wrappings or packings. A large linen sheet, generally doubled, or even four-ply, is soaked with cold water, well wrung out, and then spread upon a woollen blanket. The patient, stripped naked, is put first into the wet cloth, and then tucked into the blanket. It is desirable to make the wet sheet extend down only from the neck to a little beyond the knees, so that only the dry blanket is wrapped round the feet. Meanwhile a second packing is prepared on a second bed close at hand, or on a mattress laid on the floor. After about 10 minutes, in the later packings after from 15 to 20 minutes, the patient is taken out

and wrapped up anew, and so on from three to seven times altogether.

We can form no idea *a priori* of the amount of the heat-abstractive action of such a succession of packs. The conjecture has even been hazarded that under this treatment the loss of heat is more hindered than aided.

In order to throw some light on this subject, I instituted some calorimetric experiments, in which a somewhat complex method was necessary. For details of these I must refer to my earlier communications (loc. cit. 1868, p. 162 et seq.), and in this place give a statement only of the results—viz. that a series of four successive packings, in which perfectly cold water is used, has pretty much the same extent of action as a bath of 20° C. (68° F.), and from 10 to 15 minutes' duration, and a much greater action than an ordinary cold affusion. The net effect, on account of the longer duration of the process, is less than that of a cold bath. Ziemssen and Immermann, who estimated the action from the consequent lowering of the temperature of the body, also found the effect of from four to five successive packs less than that of a gradually cooled bath, but greater than that of a cold affusion (loc. cit. p. 113 et seq.)

A cold pack is among the least unpleasant of heat-abstractive measures. The first contact with the cold wet sheet is uncomfortable for the patient, but the disagreeable feeling lasts only for a short time; and, after the lapse of a few minutes, patients usually feel tolerably comfortable. One, and generally even several cold packs may be employed without any danger, even in the case of the weakest patient, and symptoms of collapse may with certainty be avoided if we cease to renew the pack as soon as the patient, during its application, as well as in the too long continuance of it, complains of disagreeable coldness or shivering, and shows other signs of too great chilling.

Even under the most unfavourable external circumstances, the requisites necessary for a cold pack are easily procured in private practice, and patients, as well as their friends generally, consent more willingly to cold packs than to the cold bath. In hospital practice, on the other hand, the cold pack does not recommend itself as a regular method for the reduction of temperature, because, on the one hand, really more can be

accomplished with cold baths; and because, on the other, when the patients requiring such treatment are numerous, the staff of nurses would not be sufficient, while cold baths in a well-constructed hospital are attended with little trouble, and do not consume much time.

Where an effective abstraction of heat is indicated, I therefore consider the cold pack the proper method, if the external circumstances or the condition of the patient render the application of the cold bath very difficult, or contra-indicate its employment. It may the more readily be substituted for the cold bath, the less the volume of the body of the patient happens to be. For children particularly, if repeated often enough, the cold pack is perfectly sufficient.

Ziemssen and Immermann have laid down the following proportion as an approximative formula for the comparative effectiveness of the heat-abstractive methods :—

$$A : P : G : C = 1 : 2 : 3 : 4,$$

in which A denotes the net effect of a cold affusion; P that of a series of about four packings, quickly succeeding one another; G that of a gradually cooled bath; and C that of a cold bath (loc. cit. p. 117).

This estimate of the extent of the effect, principally derived from the action on the temperature of the body, coincides approximately with that obtained by us from calorimetric investigations, and may very well serve as a sufficiently reliable guide for practice. In the individual case many other variations may be produced by change in the temperature of the water and the duration of its application. Still the employment of the ordinary cold bath is by far the most effective heat-abstractive method. To this the gradually cooled bath comes next, and if in this last the cooling is carried sufficiently far, and the patient is then kept in the bath for some time longer, the full effect of an ordinary cold bath may be reached.

Other Methods of Reducing the Temperature.

As regards the extent of action of cold spongings and compresses, ice bladders, &c., no accurate investigations have

as yet been made. Many physicians seem to think that cold baths may be superseded as heat abstractors by such methods; but this is a misconception of which it is easy to get rid, if we simply calculate how much heat we can possibly abstract from the body by such processes even in the most favourable case. It has been found that frequently repeated cold spongings and compresses, ice bladders, &c., are of next to no value as contrasted with the action of a cold bath. And the same result is obtained when we directly observe their action on the temperature of the body. It is only when the patient is laid out at full length upon cushions which have been filled with a freezing mixture of ice and salt, the temperature of which amounts to about − 10° C., that, as Leube[1] has shown, a real lowering of the temperature is effected.

The weaker heat abstractors are, of course, by no means to be rejected. They may in certain circumstances be a valuable auxiliary, and in slight cases, in which the indication for an energetic heat abstraction does not exist, they may be employed, and the rather that they are for the most part very agreeable to the patient. It was a step in advance which was made last century, when it was found out that we might without hesitation bathe the face and hands of a fevered patient with cold water; but it would be a serious mistake if, under the idea that we might effect a material result by means of the milder methods, we should in consequence neglect the more effective methods of heat abstraction in any serious case.

The ice bladder is, on the contrary, of great importance as a local heat abstractor. By means of it we can protect a particular part of the body in a very thorough way against the effect of a too high temperature. Thus it may prove of especial service in diminishing the risk of paralysis of the heart. In cases of fever, in which no extreme degree of feebleness of the heart has appeared, the prolonged application of the ice bladder to the precordia has, as a rule, the effect of lessening the frequency of the contractions of the heart, even when the temperature of the body is in consequence not perceptibly lowered. By the application of the ice bladder to the head, febrile

[1] *Deutsches Archiv für klin. Medicin*, vol. viii. 1871, p. 355 et seq.

derangements in the functions of the brain may also be lessened.

Abstraction of heat from the internal organs by means of cold drinks, the swallowing of ice, by cold clysters, and the like, produces a lowering in the temperature of the body almost as much as corresponds to the quantity of heat necessary for the calefaction of that which has been swallowed or injected. Although the general effect of such heat abstractors, in so far as moderate quantities of them are introduced, is not of any great consequence, yet they have this advantage, that in such cases a regulative rise of the production of heat does not take place, so that consequently the whole result of the heat abstraction takes effect as a pure loss of heat. A frequent repetition of them, so far as they do not cause inconvenience to the patient, is on that account strongly recommended.

Influence of the Period of the Day.

In a previous part of this work (p. 24) several factors have been referred to as co-operating in individual cases of heat abstraction in determining the resultant lowering of the temperature, and contributing to the net effect. Of especial practical importance is the influence of the period of the day. The fluctuations of temperature by day, such as we find in the healthy subject, are wont to show themselves more or less distinctly in cases of continued fever; so that in the fever patient the temperature, as a rule, also sinks during the night, and rises during the day. And as regards the heat-abstractive processes, there are many experiences which seem to point to the result that they have on the average a greater effect when the temperature of itself is on the point of falling, and, on the other hand, a less effect when the temperature is on the point of rising.

Currie has given it as his opinion that the safest and most favourable time for the affusions is when the exacerbation is at its height, or immediately after, when it begins to give way again; and for this reason, he says, he prescribes the affusion between six and nine o'clock in the evening (loc. cit. vol. i. p. 15).

Brand found the lowering of the temperature after a bath

to be in general less when the exacerbation was at its height (loc. cit. 1861, p. 107 et seq.) However, the observations communicated by him on the decrease of the temperature after the bath (about 250 observations on 5 patients with enteric fever) do not give evidence of a distinct influence due to the period of the day.

Ziemssen and Immermann, who compared 436 separate observations on typhoid patients, found, with Currie, that the baths effected a greater lowering of the temperature towards seven o'clock in the evening than at any other hour of the day. However, no influence of any consequence connected with the time of day, affecting the extent of the immediate action of the bath, could be detected; and the baths used during the night, the number of which was, however, comparatively small, showed no really greater effect (loc. cit. p. 99 et seq.) On the contrary, an important difference was seen in regard to the length of time during which the lowered temperature, brought about by means of the baths, persisted. After baths taken between 7 in the morning and 3 in the afternoon the temperature was, on the average, after from 6 to 7 hours, pretty nearly at the same height at which it was before the bath. After baths given between 6 and 9 in the evening, the continuance of the action in this sense amounted on the average to from 10 to 12 hours, and, after baths given at night, to from 6 to 8 hours (loc. cit. p. 102 et seq.) Here, however, we must take into account that this difference in the time, during which the temperature remained lowered, is, in part at least, caused simply by the fluctuation in the temperature of the body due to the time of day. Even if no bath had been used, the temperature would as a rule be lower during the night than in the evening, and a comparatively long time would pass until this would have approximately reached the height of the previous evening's temperature. We might, still further, investigate what would be the result if we should reckon, as the duration of the action of the bath, the time during which, in consequence of the bath, the temperature is lower than it would have been at the same time of the day without a bath beforehand.

The investigations which Leichtenstern (loc. cit.) conducted

in the clinic of Lindwurm at Munich, and in which nearly two thousand separate observations on typhoid patients were included, refer only to the time of the day between 8 in the morning and 8 in the evening. During this time determinations of temperature were made every two hours, and each time, if the temperature showed the corresponding height, a bath was given. The comparison of the determination of temperature following the bath with that preceding it gave approximately a standard by which to measure the effect of the bath. It was found that at 10 in the forenoon, and at 2 and 4 in the afternoon, the action of the bath was on the average weaker than at other hours. Upon the action of baths employed during the night no observations were taken.

Towards the investigation of the question respecting the influence of the time of day upon the object of the bath, and especially the possible differences between that of day and night, I may avail myself of the observations of the clinic in Bâle, in which, since 1867, in all cases of fever in any measure severe, I had the determinations of temperature taken and eventually baths introduced at night as well as by day.

The observations contained in the clinical histories of the patients were arranged in statistical form, after the method of Leichtenstern. A determination of the temperature in the axilla was systematically made every two hours, and, whenever it reached or exceeded 39° C. (102·2° F.), a bath of 20° C. (68° F.), and of 10 minutes' duration, was given. The temperature was only in exceptional cases determined again immediately after the bath; the next determination took place usually two hours after the preceding one, and therefore perhaps one hour and three-quarters after the bath. The difference of temperature observed is accordingly dependent on the direct action of the bath, as well as also on the duration of it. But a gross result, which, besides the direct action, also exhibited in some degree the duration of it, might appear pre-eminently serviceable for the determination of the practical value of the bath. In most cases the temperature had, after two hours' time, not yet risen again to its former height; the lowering observed was regarded as a positive effect. In certain cases the temperature previous to the bath was reached again or even exceeded;

and such a rise in the temperature was regarded as a negative effect, along with an unfavourable prognosis.

The determinations of temperature were made by trained nurses, and frequently checked by the physicians. Hence, although the numbers separately do not possess the accuracy that is desirable for many scientific purposes, yet we may be sure that on the whole no errors damaging to their statistical value exist. The circumstance, that the height of the temperature in the axilla is usually somewhat under the actual temperature, is compensated for by this, that it is only the difference between the two determinations which is taken into account.

A selection was made from the observations, in as far as all milder cases of sickness, in which baths were but seldom employed, were eliminated, as well as also those stages of the disease during which the baths were only rarely employed. In order to have a definite basis for the selection, it was further laid down, as a rule, that an observation was to be used only where four baths at least had been employed during the 24 hours, either preceding or following it. Since what had to be done was to determine the difference of the action of the baths at different periods of the day, it would have been manifestly absurd if we had also resolved to include the days with few baths, since these few baths were almost always administered at the same period of the day, that is to say, late in the afternoon, or early in the evening, at the time when the temperature was highest. Thus the whole of the observations refer to cases and periods of obstinate fever, such as could be kept within bounds only by frequently repeated baths. Obviously all observations were also eliminated in which, as occasionally happened, not exactly two hours, but a longer or shorter time elapsed between the two determinations of temperature that were to be compared. We may also mention that only observations on adults were made use of.

It appeared sufficient to divide the day into twelve different periods, and since by far the greater number of determinations of temperature was made in the odd hours of the day, those so made were therefore selected. The observations which were made at the evening hours of the day were divided into equal parts, and the one added on to the preceding, and the other to the suc-

ceeding, odd hour. 6,356 separate observations from 1868 to 1871, and which had been made on 199 patients suffering from enteric fever, were employed. If we take into account the reduction of temperature which is observed about two hours after the bath, we obtain for the baths employed at the different hours of the day the following average estimates :—

Time of the bath:	Night. 1	3	5	7	9	Midday. 11	1	3	5	Evening. 7	9	11
	0·54	0·58	0·58	0·55	0·32	0·20	0·20	0·23	0·27	0·40	0·39	0·55

From the observations taken collectively, there results as the average a lowering of the temperature to the extent of 0·37° C. (0·67° F.) It appears that between 7 in the evening and 7 in the morning the action is greater than this mean estimate, and that, on the other hand, between 9 in the morning and 5 in the afternoon the action remains under the mean estimate. On an average, therefore, the baths have a greater action during the night than by day.

There is, however, one more circumstance to be taken into account, which may possibly have an influence on the result. In many of the cases experimented upon quinine had been at times given in large doses, and since the dose of quinine had been administered very frequently in the late hours of the afternoon, between 4 and 7 o'clock, it was natural to suppose that the action of the bath, which was on the whole stronger during the night, might in part be due to the action of the quinine. All the observations, therefore, which were made during the 24 hours immediately succeeding the administration of a dose of quinine were excluded. After the deduction of these, 4,708 observations remain, of which the following numbers give the average value :—

Time of the bath:	Night. 1	3	5	7	9	Midday. 11	1	3	5	Evening. 7	9	11
	0·45	0·51	0·52	0·54	0·29	0·18	0·20	0·23	0·26	0·31	0·33	0·43

Here the numbers are to a trifling extent smaller; but the result, otherwise, is not materially different. The mean of the observations amounts to 0·33° C. (0·6° F.), and the numbers for the individual hours are above the average from 11 in the evening to 7 in the morning, and under the average from 9 in the morning till 7 in the evening. The action of the baths appears to be considerably greater during the night than during the day.

The observations which were made within 24 hours after administering a dose of quinine yield generally larger numbers:—

Time of the bath:	Night. 1	3	5	7	9	11	Midday. 1	3	5	Evening. 7	9	11
	0·85	0·92	0·92	0·69	0 54	0·34	0·21	0·23	0·30	0·52	0·51	0·78

The average, from all the observations, amounts to 0·5° C. (0·9° F.) The action exceeds the mean, between 7 in evening and 9 in the morning; it is less than this between 11 in the forenoon and 5 in the afternoon.

The variation between the results by day and by night is, obviously in consequence of the action of the quinine, still larger than we find in the other observations.

We infer that the immediate empirical result which is deducible from these comparisons is, that, in enteric fever, *the average action of the bath, so far as that shows itself by an effect on the temperature of the body two hours or so after its administration, is greater during the night than during the day.* We shall again refer to this result further on, when we come to discuss the indications more in detail, and will content ourselves, for the present, simply to call attention to this: that if we prescribe baths only during the day, and not also during the night, we lose the advantage of the period of their greatest action.

The question of the cause of this variation in the action of the bath at different times of the day is one of great interest theoretically. In general the action of the bath is apparently greater during those hours of the day in which the temperature is wont to fall spontaneously in consequence of the daily variations; and it is less at those hours in which the temperature inclines spontaneously to rise. This, therefore, gives rise to the reflection, whether the diversity in the action which is observed be not due simply to this, that the effect of the bath is combined with the daily variations which take place at the same time. If no bath were taken, a perceptible lowering of the temperature of the body would on an average result in the course of two hours in the night time, while during the day there would be a rise in the temperature. Thus, the temperature-reducing action of the bath during the night, which is increased

by a certain amount, must appear lessened during the day by a certain amount. The question now arises: Does a difference in the action of the bath remain when we eliminate the spontaneous daily variations of the temperature of the body?

In order to answer this question we must find out how much on the average the temperature of patients suffering from enteric fever inclines spontaneously to rise or fall, as the case may be, within two hours at the different periods of the day. We do not as yet possess any absolutely accurate investigations on this point which yield data adequate to a statistic statement of results. With a view to obtain a provisional basis I have arranged in a statistical form 626 observations of my own, all of which refer to severe cases of enteric fever at the height of the disease, and on days in which no medicines were being administered; and I have added 207 observations besides, taken from various papers which chanced to fall into my hands. The following comparison of the mean value obtained, supplies to some extent the elements for the construction of the mean daily curve in the case of one suffering from enteric fever, while it shows how much on the average the temperature naturally rises or falls during any two successive hours at different times of the day:—

	Night.					Midday.		
Time:	1	3	5	7	9	11	1	3
	−0·01	−0·07	−0·14	−0·09	+0·15	+0·31	+0·17	+0·03

		Evening.		
Time:	5	7	9	11
	−0·03	−0·11	−0·16	−0·05

If we accordingly assume that the numbers for the average action of the bath in the different hours of the day, as given in the second table on p. 42, are in reality made up of the action strictly due to the bath and to that resulting from the changes of temperature that occur spontaneously, then, by eliminating the spontaneous variations we are able to determine the exact effect of the action of the bath alone. By this means we obtain for the latter the following numbers:—

Time of	Night.					Midday.			Evening.			
the bath:	1	3	5	7	9	11	1	3	5	7	9	11
	0·44	0·44	0·38	0·15	0·44	0·49	0·37	0·26	0·23	0·20	0·17	0·38

The numbers for the majority of the hours are so slightly different that we may feel inclined to regard as accidental the deviations which appear, and to account for them on the ground that the number of the observations which were employed to determine the spontaneous variations is comparatively small. Only from 3 in the afternoon to 9 in the evening shall we be obliged to assume that the bath has less effect.

The comparisons we have as yet made all refer to observations on patients suffering from enteric fever, but the same influence of the time of the day on the action of the bath is to be remarked also in other cases of disease that are accompanied with continuous fever. In the following table I give the results of statistics, less extensive however, on the action of the bath in acute croupous pneumonia. It is founded on 324 separate observations which wholly refer to cases attended with severe fever, and to experiments on days in which no other remedy was tried. The comparison was made exactly in the same way as in the observations on enteric fever. The following are the average numbers:—

Time of	Night.				Midday.			Evening.			
the bath : 1	3	5	7	9	11	1	3	5	7	9	11
0·27	0·29	0·34	0·35	0·37	0·09	0·05	0·16	0·26	0·31	0·32	0·35

The average of all the observations amounts to 0·25° C. (0·36° F.) It appears that baths have on the whole a somewhat less effect in pneumonia than in enteric fever: and it may be remarked here that the fever of pneumonia usually offers a greater resistance to many other antipyretic agents as well. The influence due to the period of the day is the same as in enteric fever, i.e. the time of the least action of the bath is at midday and in the afternoon, although the time during which its action is above the average is of somewhat longer duration.

THE INFLUENCE OF SEX.

If we divide, according to the sex of the patient, the 4,708 observations which refer to patients suffering from enteric fever, and to experiments on days in which no other antipyretic measure was used, we have 1,924 observations on male and

2,784 on female patients. These give for the different periods of the day the following mean values:—

Time of the bath:	Night. 1	3	5	7	9	Midday. 11	1	3	Evening. 5	7	9	11
Males:	0·50	0·55	0·69	0·72	0·36	0·25	0·26	0·35	0·31	0·36	0·30	0·50
Females:	0·42	0·48	0·41	0·45	0·26	0·14	0·15	0·14	0·22	0·27	0·35	0·37

With only one exception the action of the bath at all hours of the day appears greater in the case of males than of females. The average of all the observations amounts for the males to 0·40° C. (0·72° F.), and for the females to 0·28° C. (0·5° F.) This corresponds entirely with that of the observations of Leichtenstern (loc. cit. p. 51 et seq.), and, as regards the explanation too, we agree with this observer when he assumes that in the female the interior of the body is somewhat better protected against a lowering of the temperature in consequence of the usually greater development of subcutaneous fatty tissue. In the case of pneumonia, also, the action of the bath is somewhat greater on the average on males than on females. The average of all the observations amounts in males to 0·27° C. (0·49° F.), and in females to 0·19° C (0·34° F.)

Other Effects of the Abstraction of Heat.

Besides the lowering of the temperature of the body, which takes place as the primarily contemplated result of an energetic heat abstraction, many other effects are observed at once as accompaniments and as consequences of it, of which we propose here to refer to those that are important antipyretically. We shall mainly discuss the effects of cold baths, including those of a single bath as well as those of a succession of baths.

The first effect of a cold bath consists in an acute feeling of chilliness, and this first sensation, which is usually very unpleasant to a healthy subject, is felt quite as much by a person who is ill, and perhaps even in a still higher degree. Even patients who, when suffering from the feeling of excessive heat, crave for something cooling, and delight in the bath, experience a sense of discomfort for the first moment or two after they enter the water, from the sudden action of the cold. In this

case there is a strong sense of oppression. The breathing is interrupted and laboured, the respirations few and for the most part very deep. Gradually, with the abatement of the keen sensation of chilliness, there arises a condition which, though not altogether free from discomfort, is nevertheless quite endurable. The breathing continues irregular, the respiration is partly superficial and rapid, but between times also deep and sighing. In the further course of the bath, shivering sets in, in many cases soon, in others later, which by degrees becomes stronger, and may, when the bath is continued too long, issue in violent rigors with chattering of the teeth. This last stage, which corresponds with the advance made by the cooling on the interior of the body, and especially with the cooling down of the outer layers of muscles, is in its full development extremely painful for the patient. It sets in, on the average, sooner in the case of spare subjects than in the case of those who possess, in an abundant subcutaneous fatty tissue, a better defence against the cooling down of the interior. It is generally advisable to end the bath before the violent rigors begin. What we have said in reference to the action of the bath, shows that it is very severe treatment for the majority of patients, especially if the baths have to be often repeated; yet most patients, those even belonging to the less educated classes, are capable of being persuaded by reason, and they willingly submit to this mode of treatment, because it is easy to convince them of its suitability or necessity, and because they know that when it is a struggle for life, the liking of the patient is only of secondary importance. If, in dealing with the patient, while we do not conceal from him the great discomfort of the baths, we at the same time require his consent to their use on the ground of necessity, we shall more easily persuade him than if we seek to deny the discomfort of them. Where the physician possesses the necessary authority, and the patient is convinced that nothing disagreeable will be required of him which is not necessary, such a thing as a patient refusing to take the prescribed baths cannot happen even in private practice. Yet even in this respect we may and ought to treat each case on its own merits, and with patients on whom the baths act very powerfully we ought to reduce the number to the minimum permissible,

or else to employ those which are less uncomfortable in the first moment of their action, viz. gradually cooled baths. On the other hand, it has not unfrequently happened to me that patients who had already had experience of the beneficial action of the bath on their general condition, or expected from its more frequent repetition a quicker or a more certain recovery, have begged me to consent to a repetition of the baths, even at times when there were as yet no indications requiring their adoption. It must be mentioned that the greater number of patients, after being some time accustomed to them, bear the baths more easily than at first, provided they have not to be too frequently repeated. We need not hesitate, therefore, as a rule to prescribe in course of time baths that are somewhat colder. With certain patients the feeling of intense cold and the shivering after the bath continue longer than usual, and in these cases it is advisable to moderate the duration and the number of the baths as much as possible. In certain circumstances we may feel forced on that account to suspend the use of them.

The superficial arteries suffer very great contraction under the influence of the cold, and in consequence of this the radial pulse becomes hard and small, and often barely perceptible, during the bath; the skin shows the so called goose skin (*cutis anserina*), and is usually pale, but sometimes, especially when the baths are long continued, it becomes pretty strongly reddened and generally somewhat livid. Even for some time after the bath the contraction of the superficial arteries continues, and it is only as the temperatures of the exterior and interior of the body become equalised, and the feeling of heat returns, that the pulse becomes gradually fuller and softer. The pulse rate is as a rule less after the bath, when the patient has again become quiet, than it was before it. As long as we continue the bath treatment the pulse rate usually continues moderate throughout the entire period of the disease. The excessive increase of the rate, accompanied with less energy in the contraction of the heart, which is of such serious prognostic import as a symptom of dangerous weakness of the heart, happens with less frequency. On the whole the most important advantage of the bath treatment consists in this: that in cases where it is begun early

enough, and conducted with sufficient thoroughness, the heart is less violently affected by the rise in the temperature, and the higher degrees of cardiac debility do not so easily take place. In fact, by means of it the greatest danger connected with the fever is effectually lessened, and this circumstance plays a most important part in the diminution of the death rate, so far as that is due to the cold water treatment. Another thing is to be especially noted here—that, in consequence of the better sustained capability of the heart for work, the serious complications which result from weakness of that organ, or whose appearance is favoured by this weakness, are considerably diminished in their frequency. To this class, for instance, belong the hypostases and thromboses, especially also coagulation of the blood in the heart, and the consequent embolisms and their effects; also œdema of the lungs, and finally the inclination to total collapse from comparatively insignificant disturbances.

The influence of baths on the cerebral symptoms connected with fever, as also on the aggregation of symptoms, which is usually characterised as the typhoid condition, is very obvious. If the bath treatment is carried out consistently from the first, these symptoms in most cases do not come to maturity; and even in the so called typhoid diseases (*typhöse Krankheiten*) the typhoid (*typhöse*) symptoms are absent throughout their entire course. In cases in which serious brain symptoms have already set in before the patient has been subjected to treatment, they usually exhibit a perceptible improvement after the first bath. Patients who are delirious, or who are overcome by a strong tendency to sleep, not infrequently recover full consciousness after the bath. In other cases, indeed, in which a serious typhoid condition (*status typhosus*) has already existed for some time, anything like a speedy removal of this is not possible, and would not take place even if the disease and fever were suddenly to cease; but even in these cases, under the continuance of the cooling treatment, a gradual improvement of the psychical functions usually results. With the decrease of the brain symptoms, instead of the previous restless, sleepless state, or that of unrefreshing dozing, the patient usually now enjoys tranquil and invigorating sleep. The same thing hap-

pens with the other symptoms which together constitute the clinical picture of the typhoid condition (*typhösen Zustandes*). The excessive dryness of the tongue and lips, the thick coating on these parts, as also on the teeth and gums, for most part do not appear at all if the case is treated earlier ; and if these symptoms have already manifested themselves before the patient comes under treatment, they become less marked from day to day. A radical improvement appears in the general condition too, and the patient himself has usually the feeling that he is recovering. It is only with the return of consciousness, however, that many patients first become fully aware of their illness and its accompanying pains; and, on the whole, it is certainly not to be denied that a patient who goes through a severe attack of enteric fever in a soporific state without treatment, or who even dies in consequence, experiences much less pain and discomfort than a patient who by means of heat abstractions has been brought successfully through the critical weeks of the disease. It scarcely ever happens that the patient passes his stools or urine involuntarily, and this very circumstance not a little reconciles those in attendance to the greater demands which are made on them by being obliged to take the temperature so frequently, and the attention they have to bestow on the baths. The favourable action of the treatment, which can be seen at a glance, contributes still more to the pleasure which they feel in their work, even although the greatest exertions have to be undergone by them in carrying it out.

The remark has been often made that a sick ward in which numerous severe cases of fever are being treated by the methods of heat abstraction produces a very different impression from one in which this antipyretic treatment is not adopted. Instead of patients in a state of severe prostration, apathy, somnolence, or delirium, who are fast sinking and pass urine and fæces involuntarily, there are, as a rule, only patients in a state of perfect consciousness, who give a correct answer when spoken to and interrogated, and in whom any derangement of consciousness there may happen to be is so inconsiderable that it can only be detected by close scrutiny of their psychical condition.

'The very appearance of the typhoid patient,' says Jürgensen, 'is the best recommendation of the water treatment, and nothing grieves me more than the impossibility of translating this convincing testimony of the senses into an objective, permanent expression.'

The favourable action which the cooling treatment exercises on the cerebral symptoms has contributed more than anything else to produce the conviction that these symptoms, so far as they are peculiar to the fever, are merely results of the rise in the temperature. In fact, no one who has himself seen how the prevention of the continuously high rise in the temperature of the body, even in the so called typhoid diseases (*typhöse Krankheiten*), is quite enough to deter the appearance of these symptoms, and how in many cases where they already exist the simple cooling of the body has the effect of diminishing them, can any longer doubt the dependence of these on the height of the temperature. There is no mistake, however, that the violent stimulation of the sensory nerves in the cold bath, and the strong shock to the cerebral organ caused in consequence, tend also in many cases to excite the brain to energetic action, so far as such a thing is still possible.

A further important result of the bath treatment is that by means of it the tissues of the body are to some extent protected from the deleterious action of the rise of the temperature. In consequence of the parenchymatous degeneration which takes place in every continued rise of the temperature of the body, the organs and tissues in severe cases of fever show a greater tendency to dissolution and a less resistance to what would injure them; and, in a continued high fever, there arises in the end a state in which the least mechanical or other influence sets up rapid necrosis or gangrene of the part attacked. The pressure of the bed produces sores; the pressure of a tooth may cause necrosis of the buccal mucous membrane; wounds and ulcers, which in a healthy person would heal quickly, exhibit during the continuance of a severe fever no tendency to heal, eat more deeply in, and assume the so called phagedenic character. This inclination of the tissues to break up may be increased still further if, as the result of weakness of the heart,

the circulation and the consequent nutrition of the tissues become at the same time deficient. All these serious consequences of the rise of temperature, which in individual cases so often cause the death of the patient, occur less frequently under the cold water treatment; and this explains how it happens that under it the complications and *sequelæ* are actually less frequent, and that also the convalescence is on the average more rapid.

Some more particulars may be introduced here, and especially some statistical data in regard to the frequency of certain complications and *sequelæ* in enteric fever, as observed in the hospital at Bâle, both before and after the introduction of the cold water treatment systematically applied. In these data I notice especially that, among the cases after the introduction of this method of treatment, not only those are recorded in which it was actually carried out, but also those in which, from some reason or other, it was not gone through with, or which came under treatment with their respective complications. I remark also, that with the introduction of the cold water treatment the history of the cases was more fully kept than before, so that accidental non-observance of a complication is more likely to have occurred before this treatment was introduced than after it. Otherwise, such statistics as these, which do not take much account of the individual cases, or make an accurate distinction between the degrees of intensity in the several complications, must always be regarded as comparatively crude, and permit only the most prominent features to stand out with any measure of clearness.

It was at one time a matter of apprehension with some, as it not unfrequently still is with the laity, lest the use of the cold bath should encourage the appearance of *affections of the respiratory organs*. And in many cases it actually happens, through the influence of the cold on the skin, and principally, I believe, through the deep inspirations it causes, that more or less violent coughing is induced. This happens especially with patients who are suffering from *catarrh of the respiratory passages*. These spasms of cough do no harm, and hardly bring any material discomfort with them; and, in particular cases in which collapse of the lower portion of the lung is threatened, the

quickened respiration may even chance to be of service. Moreover, the bath does not tend to increase catarrh in the respiratory passages; on the contrary, as is also brought out, for instance, in the statistics of Hagenbach,[1] the higher degrees of bronchial catarrh occur less frequently in typhoid cases which are treated with the bath. Even the other complications in the organs of respiration occur still less often, and pass off more readily. Of *lobar and lobular pneumonia* taken together, there were in the hospital of Bâle, *before* the introduction of the cold water treatment, 60 cases, out of 861 patients with enteric fever, of whom 30 died; *after* the introduction of that treatment, out of 559 such patients, 36 cases, of which 14 died. From this it appears that the frequency of these affections formerly amounted to 7 per cent., and the mortality in the case of patients affected with them to 50 per cent.; afterwards the frequency amounted to 6·4 per cent., and the mortality to 39 per cent. The frequency of pneumonia has, according to these results, diminished only to an inconsiderable extent, while the mortality of those attacked by it is clearly less. Of condensations of the lungs, which were described as *hypostases*, there occurred before the cold water treatment 64 cases—from among 861 patients with typhoid fever—of whom 37 died; and after the cold water treatment, from among 559 patients, there were 36 cases, of whom 13 died. According to this the frequency of the hypostatic condensation amounted formerly to 7·4 per cent., and the mortality to 58 per cent.; afterwards the frequency amounted to 6·4 per cent., and the mortality to 36 per cent. In the hypostases, accordingly, the frequency as well as the mortality has diminished. If we take all the *condensations of the lungs* referred to together, the pneumonic as well as the hypostatic, we may make use of two years more of cold water treatment. Out of 861 typhoid cases before the introduction of the cold water treatment, there were 124 with condensations of the lungs, of whom 67 died; and after the introduction of that treatment, out of 882 cases of typhoid, there were 96 with condensations of the lungs, of whom 33 died. Thus the frequency of this complication amounted to

[1] Liebermeister and Hagenbach, *Aus der medicinischen Klinik zu Basel*, p. 75. Leipzig, 1868.

14·4 per cent., and the mortality resulting from it, before the cold water treatment was used, to 54 per cent.; after its introduction the frequency amounted to 10·9 per cent., and the mortality to 34 per cent. According to this, the frequency as well as the mortality had decreased to a considerable extent. Of infarcti with fatal issue, there occurred formerly, out of 861 typhoid cases, 13; afterwards, out of 882 such cases, 3; of gangrene of the lungs, there were formerly 10; afterwards, 4 cases. Of pleurisy, out of 861 cases there were observed formerly 35 instances, amongst which were 14 deaths; afterwards, out of 882 cases, 29 instances, with 7 deaths. Thus here also have we a decrease of the frequency and the mortality.

The energetic contraction of the peripheral arteries as it takes place in the cold bath, and the consequent deficiency of blood in the external parts of the body, must necessarily cause a flow of blood to the internal organs; and it can hardly be doubted that, through this driving inwards of the blood, there must be a greater tendency to the occurrence of ruptures of the vessels and hæmorrhages. On the other hand, it is conceivable that under the cold water treatment the frequency of hæmorrhages may possibly be lessened through the limiting of the parenchymatous degeneration of the vessels and the organs. Which of these two actions is the more effective, and to which side the balance inclines, can only be determined by experience. The question as regards intestinal hæmorrhages in enteric fever is a pre-eminently practical one. Among the patients suffering from this fever treated by me in the hospital at Bâle before the introduction of the cold water treatment, out of 861 cases there were 72 with intestinal hæmorrhage = 8·4 per cent.; after the introduction of that treatment out of 882 cases there were 55 = 6·2 per cent. According to this, intestinal hæmorrhages have actually been less frequent in the hospital at Bâle since the introduction of the cold water treatment.

Since decubitus is to a surprising extent connected with fever, it may be anticipated *a priori*, that a consistent antipyretic treatment would exercise a perceptible influence on its frequency and its intensity. And this has, in fact, been found to be the case. Out of 861 typhoid cases before the introduc-

tion of the cold water treatment, there were 88 of decubitus, with 36 deaths; out of 882 cases after its introduction, there occurred 71 of decubitus, with 23 deaths. Thus the frequency of decubitus amounted previously to 10·2 per cent., and the mortality to 41 per cent. of those attacked by it. Afterwards the frequency amounted to 8·1 per cent., and the mortality to 32 per cent. The difference in reality is considerably greater still than appears from these numbers; since in the antipyretic treatment the serious forms of decubitus occur much more rarely. We may state further that, among the patients treated with the baths, in individual cases (four out of 800) superficial gangrene appeared in the skin of the toes, a complication whose origin, as Jürgensen also (loc. cit. p. 33) points out in one of his cases, is possibly favoured by the contraction of the arteries on account of the cold.

Of other complications which are occasioned by the parenchymatous degeneration of the tissues, or whose origin is at any rate favoured by it, I have still to mention the secondary purulent parotitis. While in the hospital at Bâle there occurred, before the introduction of the cold water treatment, out of 861 typhoid cases, 10 of purulent parotitis; afterwards there occurred out of somewhat more than 1,100 cases only two.

The rare occurrence of the more serious psychical disturbances is another fact especially noticeable in connection with the cold water treatment. In the following comparison we have disregarded the slight disturbances which occur, especially during the night, and are soon over, and tabulate only those cases in which the derangements are of notable duration or intensity. We include delirium of every kind—on the one hand, states of excitement, and moderate degrees of these if they were of long duration, as well as the temporary and more violent excitement up to furious delirium or maniacal attacks, and, on the other hand, states of depression, from simple muttering delirium down to absolute *sopor*. Before the introduction of the cold water treatment, out of 861 typhoid cases, 161 of more serious disturbances of the psychical functions were observed = 18·7 per cent.; after the introduction of that treatment, out of 882 such cases there were 97 = 11 per cent. A still greater disparity appears if we leave out of account the

patients in whom these derangements were manifest before undergoing the treatment. The statistics lying before me admit of this separation at least for the greater majority of the cases. We have thus, before the introduction of the cold water treatment, among 820 patients, 120 cases = 14·6 per cent.; after its introduction, among 727 patients, 50 cases = 6·9 per cent.

The question as to the influence of the cold bath on tissue metamorphosis and heat production is one of great importance. It has been already stated in a previous portion of this work (p. 19), in our discussion of the theory of heat abstraction, that from all we as yet know of the matter, the fever patient is affected in the main in these respects in the same way as a man in health. The regulation of the heat, though in somewhat lessened activity, still continues even in the case of the fever patient; and during the bath there results an enormous rise in the production of heat. After the bath the condition of the temperature of the body appears to point to this conclusion, that a compensatory lessening of the production of heat follows the preceding rise. To this variation in the temperature corresponds also the production of carbonic acid, which likewise appears to be analogous to what we observe in the healthy subject. In the healthy subject there follows during the cold bath an increase of the production of carbonic acid, corresponding to the increase of the production of heat, and the elimination of carbonic acid during the bath rises considerably above the normal; but a portion of it which corresponds to the greater production of heat is eliminated after the bath, and this elimination begins immediately after the bath and continues for some time at a high rate, and it is not till after from perhaps 20 to 50 minutes that it returns to the normal, or, as happens in most cases, falls to somewhat under that point.[1] Even in fever patients I found in two experiments the elimination of carbonic acid considerably greater during the bath than before it.[2] As to what occurs after the bath, I possess no observations of my own on fever patients. Schroeder, who instituted investigations in the clinic of Vogel in Dorpat, found that the elimi-

[1] Vide Liebermeister, 'Untersuchungen über die Kohlensäureproduction bei Wärmeentziehungen,' *Deutsches Archiv fur klin. Med.*, vol. x. 1872, pp. 89 et seq., 420 et seq.

[2] Ibid. p. 452.

nation of carbonic acid was for the most part greatest immediately after the bath; on the other hand, he found that there was in one-half to three-quarters of an hour after the bath always a diminution of its elimination, as compared with this period before the bath.[1] It thus appears that as regards the time of the commencement and continuance of the elimination of carbonic acid after the bath, this is similar in the case of the fever patient to that of the healthy subject.

The question as to the way in which the decomposition of the albuminous substances in the tissues and juices is influenced by the cold bath is one that is still undecided. If we assume, as I have already before this tried to show elsewhere,[2] that the increase of the decomposition of albumen in fever is really only the consequence of the rise in the temperature, and that it supplies the expression for the degeneration of the tissues due to that rise; then we may directly conclude that a reduction of the febrile rise of the temperature of the body, so far as that is the result of the cold baths, must cause a diminution of the metamorphosis of albumen, and, as a consequence of this, of the excretion of urea. With this presupposition the results of the experiments of Schroeder (loc. cit.) were found to correspond, since in consequence of cold baths the amount of urea excreted in fever cases was proved to be less. Bauer and Künstle,[3] on the other hand, have quite recently deduced from a series of experiments made by them the conclusion that by means of cold baths in fever cases the excretion of urea is slightly increased.

The investigations of Bauer and Künstle have been conducted with such care that it is not possible to call in question the numerical results obtained by them, yet it appears to me doubtful whether the conclusion they have deduced from their numbers is the correct one. In the case of each patient the baths were employed only on alternate days, and in this way it turned out, beyond a doubt, that the excretion of urea was in every case greater on the days when baths were used than on

[1] 'Ueber die Einwirkung kalter Bäder auf die CO_2- und Harnstoffausscheidung beim Typhus,' *Deutsches Archiv für klin. Med.*, vol. vi. 1869, p. 385 et seq.

[2] *Deutsches Archiv für klin. Med.*, vol. viii. 1871, p. 155; *Handbuch der Pathologie und Therapie des Fiebers*, p. 316 et seq. Leipzig, 1875.

[3] *Deutsches Archiv für klin. Med.*, vol. xxiv. 1879, p. 66.

those when they were not used. If we are obliged to assume that those forces which affect the extent of the albuminous metamorphosis must show the result of their action at once by means of a change in the excretion of urea, then the conclusion which the authors have drawn from their results would certainly be unassailable. But there are numerous facts which show that the change in the excretion of urea does not usually appear until some time after the action of those forces which influence the metamorphosis of albumen.[1] This applies to people in good health. Thus, in the investigations of Schleich,[2] the increase of the excretion of urea induced by hot baths frequently did not show itself until the following day. We must assume, as is done by Schleich, either that the dissolution of albuminous bodies brought on by the rise of temperature takes some time to complete itself, or else that the nitrogenous products of the decomposition of the albuminous bodies which have been reduced to dissolution are only gradually oxidised to form the final products. In disease special circumstances may retard the appearance of this effect still longer. This being the case, it appears to me that, even in the experiments of Bauer and Künstle, there is nothing to hinder us, if we choose, from construing the results in such a way that the excretion of urea in one day might be referred to the condition of the patient on the previous day; and then these results would exhibit a lessening of the metamorphosis of albumen as a consequence of the cold baths. A final judgment in regard to the results of these experiments is, however, not yet possible, because from the data given it does not exactly appear how much time elapsed after the influence of the baths before the diminution of the excretion of urea showed itself. I therefore regard this question as still an open one, towards the solution of which a further and somewhat differently arranged series of experiments is necessary.

[1] Vide *Handbuch der Path. u. Ther. des Fiebers*, p. 316 et seq.

[2] 'Ueber das Verhalten der Harnstoffproduction bei künstlicher Steigerung der Körpertemperatur,' *Archiv für experimentelle Pathologie*, vol. iv. 1875, p. 82 et seq.

Applicability of Heat Abstraction.

The question, under what circumstances the application of heat abstraction is imperative, will be considered in the chapter in which, along with a general explanation of the way in which the antipyretic treatment should be conducted, the special indications for the employment of the several antipyretic methods will also be discussed. Here we confine ourselves, firstly, to the consideration of the question, under what circumstances heat abstraction may be employed; and, secondly, under what circumstances its application is forbidden. We may simplify this inquiry if we start from one fact which has been confirmed again and again by manifold experience under the most diverse circumstances. This fact may be summarised, perhaps, in the following proposition: *A man certainly suffers no harm from cooling of his body so long as the temperature of his body does not sink below the normal.*

This is true of the healthy as well as of the sick, and it holds good in the case of a slow cooling as well as in that of a sudden one. The sudden cooling, indeed, from which many even now think a so called cold is to be apprehended, entails in and by itself no injurious effects whatever. If, for instance, a man in health, by means of a hot full bath or a vapour bath or the like, has the temperature of his body artificially raised considerably above the normal, he may, without dreading any evil consequences, at once in his heated state take a cold shower bath or a cold full bath and cool himself as quickly as possible. The sick patient, with a rise in the temperature of his body due to fever, may also in like manner be cooled by means of a strong heat abstraction without fear of injury. Even the contra-indications to be afterwards specified refer in the main not to the cooling effect of the heat abstraction, but to other actions connected with particular methods. Even a cooling that lasts for some time entails no injurious consequences, provided that the temperature of the body is not thereby materially lowered below the normal. As is well known, the healthy subject may remain with impunity in a cold bath so long as the power of regulating the heat suffices to maintain the tempera-

ture of the viscera at its normal state. Only when the temperature of the body is materially lowered below the normal by means of a too intense or a too protracted heat abstraction would I lead neither a healthy subject nor a sick one to expect exemption from all evil consequences. On the contrary, individual experiences make me inclined to assume that in this case, according to circumstances, injurious effects may take place in partly the same way as they are believed to do when they occur as consequences of taking cold.

From what we have stated it appears that heat abstraction may be employed without hesitation in every case where there is a febrile rise in the temperature, provided there are no special circumstances, such as we shall have to specify by-and-by as contra-indications, to forbid its use. The limit regulating the intensity and the duration of the heat abstraction in cases of fever is determined solely by this, that the temperature of the body must not be materially lowered below the normal. If the heat abstraction is applied in the usual way, there is, as a rule, no danger at all that this limit can be overstepped; on the contrary, its action is usually found to be much less than what was desired. Nevertheless it is always advisable to control its action by the use of the thermometer.

The most usual mode of heat abstraction employed in cases of fever is the cold bath; and it has been shown already in our account of the calorimetric investigations on the extent of its action that it is the most effective. By these investigations this rule was established, that the temperature of the bath should not generally be higher than 20° C. (68° F.), and where possible even somewhat lower. In similar cases the same water may be used for several baths that follow upon one another, and it is then the simplest course to use the temperature of the water just as it happens to have become in the interval during which the bath remained in the room. Only in midsummer, or when from special reasons a lower water temperature is desired, should it be lowered to what it was at first, by means of cold water or the introduction of a piece of ice. No bath should exceed 10 minutes in duration. A continuance materially longer is generally uncomfortable to the patient, and might, according to circumstances, very possibly, by overstepping the limit, have

serious consequences. In particular cases, however, the bath is not unfrequently extended to 15 or 20 minutes. If weak patients are very much exhausted by the bath, and its use is followed by a chill or something of collapse, then it is advisable to reduce the time of it to 7 or even 5 minutes. A shortened cold bath such as this has always a much greater effect than a tepid bath continued much longer. For such cases the gradually cooled bath, as used by Ziemssen, or even repeated cold packs are suitable. The patient must have rest immediately after the bath; he should therefore, without being dried or only superficially so, be wrapped in a dry sheet, put to bed, which may be slightly warmed, especially at the foot; he is then lightly covered, should have administered to him, if circumstances require it, a glass of wine, and should only after some little time, provided another bath is not indicated again in the meantime, put on his shirt. In many cases it is advisable to administer a little wine also before the bath.

The less the bulk of the body of an individual is, the more in proportion will the action of a heat abstraction penetrate into the viscera. In the case of little children, and also of unusually spare people, there is on this account ground for caution, lest in a very cold bath of 10 minutes' duration the limit mentioned above may be overstepped. The appearance of a very strong chill or shivering during the bath is on this account to be attended to. In such cases the direct action of the bath should be controlled by the thermometer. In short, the duration of the bath must be lessened or its temperature made somewhat higher, or instead of the cold bath the cold pack must be used. However, it frequently happens even with children that after a very cold bath of the usual duration the temperature still continues at a very undesirable height above the normal.

The indication for the employment of heat abstraction is found in most cases when the temperature of the patient reaches or just exceeds a definite degree. Thirty-nine degrees (102·2° F.) in the axilla, or 39·5° (103·1° F.) in the rectum, has been most frequently assumed as this limit, the temperature being taken every two hours, and the bath being resorted to as often as it rises again to this height. In particularly obstinate fever we

may in this way have recourse to as many as 12 baths within 24 hours. According to this simple rule, the treatment, as I myself have applied it for several years, yields, as experience shows, very favourable results, and may therefore be recommended even still, of course under the assumption that the temperature be taken and the baths carried out by night as well as by day. The limit of temperature of the bath, moreover, must be taken somewhat higher or lower according to the idiosyncrasy of the individual case. I may mention here, too, what will be fully explained further on, that, as taught by more recent experience, I regard it as of material moment, when the use of the bath is resolved on, to take into account the hour of the day, and to see before everything that in the period between midnight and morning a very considerable lowering of the temperature of a long duration is effected.

The question, whether the application of heat abstraction is admissible in all cases of fever, or whether there are diseases in which it may not be employed, is one of especial importance. Heat abstraction has been most frequently employed till now in typhoid and typhus fevers. It was long ago employed, by Currie and his followers, for example, in scarlatina also, and that notwithstanding the risk of the suppression of the eruption which they believed they had reason to dread. They hesitated for a long time to employ it in measles, perhaps because in the majority of cases the indication for it is less pressing, but perhaps also on account of the affection of the respiratory passages, which they were afraid of aggravating by causing the patient to take cold. In pneumonia also it was with the same hesitation they risked the application of heat abstraction. There is a growing conviction, however, that a man with an abnormally high temperature never takes cold in the ordinary sense, and that neither affections of the respiratory organs, nor eruptions, nor rheumatic affections, constitute a contra-indication. Heat abstraction has been employed with advantage in pleurisy, in croupous and catarrhal pneumonia, in erysipelas, and in acute articular rheumatism.

My own experience of the action of heat abstraction refers to typhoid fever, of which I have treated more than a thousand cases with a thorough, and about a thousand with a less thorough,

application of the method, the majority in hospital and a not inconsiderable number in private practice. My experience also refers to acute croupous pneumonia, of which more than 200 cases were treated with thorough heat abstraction ; as also to small-pox, measles, scarlatina, puerperal fever, pleurisy, catarrhal pneumonia, epidemic cerebro-spinal meningitis, acute articular rheumatism, and erysipelas. Moderate heat abstraction was employed also in particular cases of violent catarrhal fever, in quinsey, and even in ephemeral fever. Indeed, I know of no case with acute febrile symptoms in which, if the rise in the temperature was considerable or lasted too long, I should consider heat abstraction unsuitable treatment.

Even in a case of hyperpyretic rise of temperature above 43° C. (109·4° F.) in a patient suffering from acute articular rheumatism, the energetic application of very cold baths was attended with temporary success, although death was not thereby prevented. Other physicians have also obtained favourable results in similar individual cases by means of heat abstraction.[1]

The temperature of the body may be lowered even in chronic fever by means of heat abstraction, as I have assured myself, particularly in individual cases of pulmonary phthisis. In chronic fever, I believe that the use of heat abstraction is the sooner indicated, the higher the temperature has risen, and the more it inclines to the character of that of a continued fever. The more, on the other hand, spontaneous remissions or intermissions appear, the more—according to the views to be set forth hereafter—do I incline to the opinion that we ought to abstain from heat abstraction in contending with the fever. The indications for methodic heat abstraction, as it has frequently been employed in chronic diseases, and in many cases with apparent benefit, seem to me to belong in general to another province than that of the therapeutics of fever.

Special circumstances exceptionally occur which render the application of heat abstraction impracticable in the usual way at least.

Any considerable hæmorrhage of the internal organs, and especially intestinal hæmorrhage in enteric fever, is generally

[1] Meding, Wilson Fox, H. Weber.

accepted as a *contra-indication* to the employment of the bath. It has been already stated that the flow of blood to the internal organs, caused by heat abstraction, may increase the tendency to hæmorrhages, although, on the other hand, the statistics that we have by no means show an increase of the frequency of intestinal hæmorrhages as a result of the cold water treatment, but, on the contrary, a decrease (p. 54). In any case where there is a tendency to intestinal hæmorrhages, the active or passive movement connected with the application of the bath is injurious. This holds good in a still higher degree in perforation of the intestine or other organs, and finally also in every case of acute peritonitis that is in any degree serious.

An important contra-indication is the presence of extreme weakness of the heart, whether this is due to a pre-existing affection of that organ, or to a complication, or to the action of the fever. If the circulation is so reduced that the extremities are cold, while the temperature in the interior continues very high, then there is no possible hope that a further cooling of the surface will have a material effect on the temperature of the internal organs; there is reason rather to fear that the further injury to the peripheral circulation will precipitate the appearance of paralysis of the heart. In less serious stages of cardiac debility, gradually cooled baths, Ziemssen thinks, are extremely helpful. It is to be remarked, however, that in cases where heat abstraction has been thoroughly employed at the right time, a critical stage of weakness of the heart does not so readily take place.

Finally, there are patients who, from idiosyncrasy, bear the baths badly, since after each they are chilly for an unusually long time, and even show an actual lowering of the temperature of the periphery. In such cases it is imperative to limit in some degree the number of the baths.

On the other hand, croupous or catarrhal pneumonia, bronchial catarrh, and capillary bronchitis, even of a high degree, also hypostases, &c., form no contra-indication to the application of the baths. It has been sometimes observed that the hypostases, which are present in some patients when they come under treatment, disappear under the use of the bath.

Menstruation in women is to be regarded as a contra-indication to the use of the cold bath only when there is no possible danger in delay; but when, on the other hand, the fever is violent and persistent, and cannot be immediately sufficiently moderated by other means, the baths are to be employed just as usual. Pregnancy and the puerperal state form no contra-indication; they rather, on the contrary, challenge us to a more thorough-going contest with the fever, on account of the greater danger attending it, while at the same time they require us to pay especial attention to the state of the circulation.

We have only to add that even in the cases in which the customary methods of heat abstraction are contra-indicated, we may often adopt others which, though less effective, are yet in such cases not without good result, such as heat abstraction from internal organs by means of a cold draught.

CHAPTER III.

ANTIPYRETIC MEDICINES.

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A large number of references and abstracts will be found in the more recent 'Jahresberichte' of Virchow and Hirsch.

Quinine.

Of all the antipyretic medicines, preparations of quinine were the first that were employed for the definite purpose of reducing temperature. The extraordinarily favourable action of this drug in malarial fever naturally led to experiments with it in other fevers; and, in fact, at the time of the first introduction of cinchona bark into practice, it began to be greatly employed as a universal antipyretic in many other febrile diseases, and especially in the gravest forms of them. The fact, however, was soon established, that in no other fever does quinine exert such a sure effect as in malarial fevers. So long as only such doses of the drug as were customary and sufficient in malarial fevers were employed, there appeared a show of reason to doubt whether a universal antipyretic action could be attributed to quinine. And numerous observers who had set about the testing of it with the greatest confidence, soon, as a result of this, pronounced it to be inactive.

Later experiences have shown that quinine has a strong antipyretic action in other diseases only when it is administered in large doses, and these doses must be considerably larger than those usually employed in ordinary malarial fevers. Such doses had been already repeatedly prescribed by individual physicians. Thus, Briquet especially had employed and recommended quinine in large doses, particularly in acute articular rheumatism, and also in certain cases of enteric fever. Yet, although in these instances, among others, it appeared that the fever and the disturbances dependent upon it, especially the changes in the circulation, and many serious cerebral symptoms were considerably lessened by such doses, the conception of the action as in reality an antipyretic one was not then possible, principally, I believe, because people were not aware of the significance of the rise in the temperature, and were not accustomed to measure temperature. It was supposed rather that the quinine exerted a specific action in acute articular rheumatism and in enteric fever, and it was considered to be the more indicated the more the fever presented distinct remissions and exacerbations, i.e. the more it approached the type of the malarial fever.

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Dietl[1] had found quinine to be effective in large doses, especially in the treatment of the serious cerebral symptoms accompanying typhoid.

W. Vogt, of Berne, was the first to employ quinine in sufficient doses, and at the same time with the distinctly expressed idea that the action was in reality simply an antipyretic one; and this he did chiefly in enteric fever and in acute articular rheumatism. Although, even in the work of Vogt (loc. cit. 1859), determinations of temperature were entirely neglected, yet the facts communicated were in other respects such that the antipyretic efficiency of quinine could hardly thereafter be called in question. More recently, A. Wachsmuth has communicated (loc. cit. 1863) some cases of typhus fever and of enteric fever that were treated by him with larger doses. Isolated communications in regard to the antipyretic action of quinine have been made also by other authors.

I have, since 1858, employed quinine as an antipyretic in different fevers, but I at first gave doses in which the antipyretic action, although it could be clearly recognised on careful observation, was nevertheless but small. Only after I became convinced from the communications of W. Vogt that I had been up to that time usually far too scrupulous in the dosage of the drug, did I by degrees proceed to administer larger doses, in which the antipyretic action, even although less accurately observed, came out distinctly. Such doses I have since continued to employ in the majority of cases of fever that have come for treatment in which there was really danger in consequence of its greater intensity or protracted duration. The experiences collected up to 1867, which decide that quinine is a universal antipyretic, were brought together in the above-mentioned work. Since then, quinine has been employed in antipyretic doses by a great many physicians, and it has stood the test well. At present, it is employed almost universally among German practitioners.

To ensure a strong antipyretic action, a dose of 20 to 45 grains is necessary in the case of adults. A solution is a suitable form in which to administer it in cases in which the patient

[1] *Wiener medicinische Wochenschrift*, 1855, No. 50.

can bear it; and this may be administered all at once, or it may be divided into several small doses, and the whole given in the course of half an hour. The sulphate of quinine can be dissolved with the addition of a little sulphuric acid. The chloride of quinine has the advantage of greater solubility; it is to be remarked also that the latter salt possesses a somewhat greater amount of the active base. With patients in whose case the administration of the solution is in any way very troublesome or disagreeable, or in whom it easily provokes vomiting, the drug is given in the form of powders wrapped up in wafers, so that 8 grains are swallowed about every ten minutes. I have for this purpose usually employed sulphate of quinine, and find in general no perceptible difference in the action of the two salts when given in equivalent doses.

In order to attain a full antipyretic action, it is absolutely necessary that the whole dose be administered within a short time—in the course of half an hour, or, at the utmost, of from one to two hours. If this is not done, and if the whole quantity administered is distributed over a longer time, the full effect is not to be expected. I should like to accentuate this point, to which Dietl has already called attention, all the more that in my earliest communications on the antipyretic action of quinine (loc. cit. 1867) I did not give it such prominence as I at length found myself obliged to do after I became convinced that the repetition of small doses was the sole reason why, in many cases observed by others and myself, the action was defective. Even when much greater quantities are distributed over a half or a whole day, it is often with difficulty that any distinct effect on the temperature of the body is observed. On the other hand, I do not repeat the dose in any case until after 24 hours, and as a rule only after 48 hours.

The cause of the slight effect of repeated small doses is this, that in such cases a sufficient quantity of the drug is never present in the blood at a given time, in order to obtain full effect. Quinine is in a comparatively short time eliminated through the kidneys.[1] Hence a strong action is to be looked for only when a large quantity is quickly absorbed.

[1] Vide H. Than, 'Ueber den zeitlichen Werth der Ausscheidungsgrösse des Chinin bei Gesunden und fieberhaften Kranken,' *Deutsches Archiv für klin.*

The occasional reluctance of the patient, as well as the circumstance that the administration of the quinine is now and then accompanied with vomiting, may render another mode of application desirable in certain cases. Although subcutaneous injection might appear to be specially serviceable, because in this form we may expect that the quinine will be more quickly absorbed, yet experiments have shown that, corresponding to the small dose which can be introduced in this way, the effect is of but small account. On the other hand, I am convinced that in the application of it in the form of clysters, for which the solution with the addition of a little tincture of opium is employed, as well as in the form of suppositories, the action is only a little less than when it is introduced into the stomach.

A full dose of quinine, as a rule, induces in the patient a loud ringing in the ears, and usually also difficulty in hearing. In unusually large doses it induces besides a quasi-intoxicated condition, with unsteadiness of movement, weakness, and trembling of the extremities, and at times a considerable sense of discomfort. These latter symptoms seldom assume a decided form in fevers when the dose is not above 45 grains, while in health they may manifest themselves after a dose which does not exceed 30 grains. What we are told of serious collapse and other alarming symptoms as the results of large doses of quinine must, I think, be relegated to the realm of fable; stories of this kind usually come from authors who have themselves never observed the action of large doses. The only form of collapse (and that occurs only exceptionally) is the collapse of reaction, as, in special circumstances, it may occur after every rapid fall of the temperature. There is in this nothing critical, but it is, on the contrary, a satisfactory symptom.[1]

We still meet with physicians who are somewhat chary of employing large doses of quinine. Where a dose of 30 grains

Med., vol. v. 1869, p. 505 et seq.; G. Kerner, 'Beiträge zur Kenntniss der Chinin-Resorption,' *Pflüger's Archiv für Physiologie*, ii. 1869, p. 200; iii. 1870, p. 93 et seq.

[1] See C. Binz, 'Ueber die angeblichen Gefahren des Chiningebrauchs,' *Deutsche Klinik*, 1871, No. 46.

or more happens to be indicated, they decide on employing at most a dose of 15 grains, and they then not unfrequently fancy that they can make up for their remissness by repeating the dose oftener—once or twice a day, say. In proceedings of this kind a satisfactory result is not to be looked for. I have up to the present time employed quinine in large doses in more than 1,500 cases of enteric fever, and in hundreds of cases of pneumonia and other diseases. The number of individual doses of 20 to 45 grains which I have prescribed in hospital and private practice amount to about 10,000. And I have not in one single instance seen any special or long-continued bad after-effects appear which I might think myself justified in ascribing to the action of the quinine. Other individual physicians, such as Jürgensen, for example, have in particular circumstances even exceeded the dose of 45 grains, which I have till now set down as the maximum, and that without observing any injurious results. The same caution is to be recommended in the employment of quinine in large doses as in the employment of every other active remedy. Even the knife of the surgeon can, in the hand of a bungler, work mischief. If we are not sufficiently acquainted with the idiosyncrasy of the patient or the peculiarity of the case, and if there is no danger in delay, it is advisable to employ at first the smaller dose of about 20 or 30 grains, and, if that is insufficient, a larger dose may be administered next time.

A considerable fall in the temperature of the body is in fevers the result of the action of a full dose of quinine, and that is sometimes accompanied by more or less abundant sweating. The fall of the temperature generally begins some hours after the administration of the drug, and the minimum is reached on the average about 8 to 12 hours after; then the temperature begins gradually to rise again; yet on the average a somewhat lower mean temperature is noticeable on the next day.

The extent of the fall in the temperature, which is caused by a definite dose of quinine, varies in different cases. It may happen that the temperature goes down to the normal after a full dose, while in other circumstances the same dose shows a far less temperature-reducing action. We are able to specify some of the circumstances on which the extent of the effect is

evidently dependent, although many others escape our observation.

The Period of the Day.—The influence of this is recognisable here, among other things, just as in heat abstraction, only generally still more distinctly. This shows itself in such a way that the lowering of the temperature caused by the quinine is wont to coincide by preference with the time when the daily temperature curve is descending. If, in a continued fever with a regular course, in which the usual daily variations of temperature are clearly present, a sufficient dose of quinine is given in the evening, a considerable fall of the temperature is to be calculated on until the following morning. If, on the other hand, such a dose is given in the morning, nothing like so great a fall is to be looked for till the evening. It may happen that the normal evening rise is not for one moment completely checked by means of it, so that until the evening the temperature not only does not fall, but it continues even to rise a little. In such cases the greatest reduction of the temperature usually does not take place till after the time of the evening exacerbation, and especially after midnight.

The following results of statistical comparisons apply to patients suffering from enteric fever, treated with 20-grain doses of the sulphate. To obtain a thorough antipyretic action, such a dose is generally insufficient; and I have employed it very frequently only in my first cautious experiments with antipyretic doses (since 1859). Yet these observations are quite fitted to decide the question of the influence of the period of the day, since what is really to be done is to compare directly the effects of equal doses.

In the comparison all observations were excluded in which the dose administered was either greater or less than 20 grains, also all observations in which heat abstractions were employed at the same time, and, finally, all those which were made in that stage of the disease when the fever had already assumed the strongly remittent or intermittent character. With these exceptions, no selection whatever was made. The temperature, as a rule, was taken in the morning between 8 and 9, and in the evening at 6. Even in the cases of which more frequent determinations of temperature are recorded, only those which were made at the stated hours were made use of.

To ascertain the influence of the period of the day, the observations were divided into those in which the quinine was administered in the evening or during the night, and those in which it was administered during the course of the day. The time between the administration of the drug and the determination of the temperature varied from four to ten hours. It is to be presumed, therefore, that in many cases the determination of the temperature did not coincide exactly with the time of the strongest action of the quinine.

Of 178 separate observations, in which 20 grains of the sulphate had been administered during the night, only in one instance was the temperature found to be the same on the following morning as on the previous evening; in every other case the temperature had fallen. But in these 178 observations the fall in the temperature on the average amounted to 1·60° C. (2·9° F.), an amount, therefore, which is much more considerable than the normal average difference between two definite hours of the evening and morning.

Out of 176 observations, made on the same cases as the above, in which 20 grs. of the sulphate had been given during the day, there were 69 in which the temperature was in consequence lower in the evening than it had been in the morning, 10 in which it was equal to the morning temperature, and 97 in which it was higher than that. Thus the usual evening rise of temperature was arrested, or instead of that a fall had taken place, by the action of the quinine in less than half of the cases. The calculation of the mean value of the difference between the temperature in the morning and that in the evening, in which positive and negative differences were allowed for, yields not quite 0·1° C. (0·2° F.) as an average increase of the temperature in the evening for the 176 observations.

The following is the result of the statistical comparison:—If in a case of enteric fever 20 grains of the sulphate of quinine are given late in the evening or during the night, we may expect on an average that the temperature will be about $1\frac{2}{3}$° C. (3° F.) lower the next morning than it was in the evening. If the same dose is given during the day, it is, as a rule, about enough to hinder the rise in the temperature which would otherwise take place towards evening.

The influence of the period of the day comes out still more clearly if we exclude the amount of the spontaneous daily variations, and if in the observations, instead of comparing the temperature of the evening with that of the morning, we regularly compare the temperature at a certain hour after the action of the quinine with that of the same hour of the previous day.

Out of 168 separate observations, in which 20 grains of the sulphate of quinine had been administered during the night, the temperature was found in 159 cases lower on the following morning than on the previous morning; only in 9 cases was the temperature higher. The calculation of the mean value from these 168 observations, in which positive and negative differences were allowed for, shows that after the administration of 20 grains of quinine during the night, the temperature on the following morning was, on the average, 0·92° C. (1·70° F.) lower than on the preceding morning; on the following evening it was, on the average, 0·69° C. (1·2° F.) lower than on the preceding evening.

Out of 148 observations, in which the same dose had been given in the course of the day, in 116 instances the temperature was found lower in the evening of that day than on the previous evening; in 10 it was found the same, and in 22 it was found higher. As a mean average value resulting from these 148 observations, it appears that the temperature in the evening was 0·43° C. (0·80° F.) lower than on the previous one. On the morning of the day following it was 0·80° C. (1·40° F.) lower than on the previous one.

The temperature-reducing action of quinine is accordingly on the average greater in the morning than in the evening; but, indeed, the time of the strongest action is so far independent of the time of the administration, that whether the quinine has been administered in the daytime or during the night, the time of strongest action coincides by preference with the time of the spontaneous morning remission. In order to obtain as strong an action as possible, we should therefore select such a time for the administration that the action may take effect principally whilst the daily temperature curve is low, i.e. in the time from midnight till the morning. And since observa-

tion shows that the strongest effect of the drug is usually visible on the average about 8 to 12 hours after its administration, the late hours of midnight or the early hours of the evening, say from 3 to 7, appear to be the best time for administering it.

The Largeness of the Dose.—This has a decided influence on the extent of the action; but we must in this connection reckon, as the total dose administered, only the quantity that is absorbed within a comparatively short time. As is demonstrable, many imperfect results are due to the circumstance that the whole quantity administered was not given in a short space of time, but distributed over too great a period; also an unusually slight effect may sometimes be due to this other circumstance, that in the particular case the absorption of the drug from the intestinal canal proceeded with unusual slowness. And for this reason the administration of quinine in solution appears (theoretically, at least) more to the purpose than the administration of it in the form of a powder or a pill.

After the administration in the evening of 30 grains of chloride of quinine in solution, Oeffner (loc. cit.) found the temperature on the average 1·6° (2·9° F.) lower the next morning than on the preceding one. If we compare this result with my observations on the average action of 20 grains of sulphate of quinine, the mean decrease of temperature will appear to be nearly proportional to the largeness of the dose.

In a careful work by Courvoisier (loc cit.), the lowering of the temperature caused by quinine is not so reckoned as to bring out the comparison of the temperatures at a definite period of the day, but to ascertain the difference between the highest temperature shortly before or at the administration of the drug, and the lowest point reached by the temperature which can be regarded as an effect of it. This method of calculation, while it is perfectly justifiable for certain purposes, and while the results of it, if the average is taken from a great number of observations, may be very easily compared with one another, must necessarily exhibit considerably higher numbers. With 30 grs. of sulphate of quinine, Courvoisier found, after an evening dose in powder, a mean decrease in the temperature of 2·15° C. (3·90° F.); after an evening dose in solution, a decrease of 2·5° C. (4·5° F.); and finally after a morning dose in powder,

a decrease of 2·17° C. (4° F.) The morning doses were usually administered between 10 and 11, and the evening ones between 8 and 10. On the basis of measurements of temperature repeated every two to three hours, the time of the lowest fall of the temperature was found to be from 10 to 11 hours after the administration of the dose; yet the extreme limits amounted to 2 and 16 hours. That the influence of the period of the day was not recognised in these observations was owing, it is plain, simply to the mode of reckoning in which the daily variations of temperature were not taken into account. The time of the greatest reduction of the temperature, which, according to the statements of the author, appears from 2 to 16 hours after the absorption of the drug, must have taken place, it would seem, just as in my observations, usually at the time of the spontaneous fall of the curve of temperature; although there is no mention of this.

The Nature of the Disease.—This also has an effect on the extent of the temperature-reducing action of quinine.

It is of especial interest that doses of quinine, from which a distinct reduction of temperature is to be looked for in fevers, induce, as in healthy persons, no perceptible lowering of the temperature of the body in patients who have no fever. There are no diseases, where fever is present, in which quinine in comparatively small doses acts in such a certain and surprising way as in malarial fever. In these cases we must ascribe to quinine not only an antipyretic, but also a specific, action. Of other diseases, enteric fever is, I believe, the one in which the antipyretic action of quinine comes out the most distinctly. The fact is due partly to this, that the spontaneous course of the temperature is in this disease comparatively regular, so that a change in the course caused by a strong therapeutic agent may be detected with comparative ease. In many other diseases, however, the fever appears to show on the average a somewhat greater obstinacy to the action of quinine. An antipyretic action indeed will always be remarked if we make accurate enough observation, and especially if a sufficient dose is absorbed in a short time. In the treatment of other diseases besides enteric fever, I have very frequently employed quinine successfully, and that not only in acute croupous pneumonia, but also in measles,

scarlatina, erysipelas, puerperal fever, acute articular rheumatism, pleurisy, peritonitis, epidemic cerebro-spinal meningitis, ulcerative endocarditis, acute miliary tuberculosis, in phthisis florida also, if this is combined with fever of an almost continued type, and finally in the symptomatic fever which accompanies suppuration. Among diseases in which the fever offers at times a very stubborn resistance to the action of quinine, we may mention acute articular rheumatism, acute miliary tuberculosis, cerebro-spinal meningitis, ulcerative endocarditis, the fever of the suppurating stage of small-pox, and many cases of symptomatic fever accompanying other suppurations. We may say in general that we have reason to expect a distinct effect from the action of quinine with the greater certainty, the more the fever corresponds to a continued type, with normal daily variations of temperature; while, contrary to the view still maintained by many, the action is usually less certain in cases in which the fever spontaneously shows strong remissions or intermissions. Where considerable irregular variations of temperature occur, the action may sometimes appear disproportionately large, if it chance to coincide with the spontaneous resolution of the fever, but it may also appear very small, or in certain circumstances be imperceptible, if it chance to coincide with a violent exacerbation.

Even in the same disease there is a difference in individual cases as regards the action of quinine. In general, the more severe the case is, the larger the dose must be to obtain any satisfactory abatement of the fever. Thus, for example, in slight cases of enteric fever, a sufficient reduction of the fever may in particular circumstances result from 20 grs.; while in serious cases about 35 to 45 grs. are necessary to secure the same effect. The action which a definite dose of quinine exerts is therefore, in some circumstances, a measure of the obstinacy of the fever, and at the same time of the gravity of the case; and in this respect the observation of the action of the quinine is of special prognostic importance.

In many diseases the action is different in the different stages; and in this respect, too, the greater action corresponds to the times when the temperature spontaneously shows a tendency to fall. In most diseases the action is greater at a

later stage than at the first, when the fever is high. In diseases with a long-continuing *stadium incrementi*, as, for instance, in enteric fever, the action is often comparatively great during the period in which the fever has not yet reached its utmost intensity.

The Idiosyncrasy of the Patient.—Finally, this must also be taken into account. Strong people generally require and bear larger doses than those who are weak, and adults larger doses than children. With this difference quinine may be employed in the case of children just as in that of adults. To obtain a satisfactory antipyretic action, according to the experience of E. Hagenbach,[1] a dose of 10 to 15 grs. is necessary for children under two years of age, one of 15 grs. for those from 3 to 5, one of 15 to 20 grs. for those from 6 to 10, and one of 20 to 30 grs. for those from 11 to 15. When we employ smaller doses, the action is often imperceptible or doubtful, and Hagenbach is rather inclined in certain cases to increase the doses somewhat. Bad symptoms were never observed in these cases, such at any rate as might have been referable to the action of the quinine. Ringing in the ears and difficulty of hearing are said to have occurred in the case of the older children, just as in adults.

In certain cases, by merely taking into account the obvious facts before us, we may often be *a priori* in a position to calculate the dose that should be prescribed with tolerable accuracy. Where any doubts exist in this respect, we must first of all try the smaller dose. I regard the action of a dose of quinine as perfectly satisfactory only when by means of it the temperature has been brought down nearly to the normal, viz. 38° C. (100·4° F.) or less in the rectum. If this is not reached under the first dose, a stronger one is given next time. If, on the other hand, as often happens, the temperature is reduced to 37° (98·6° F.), or still lower, after the first dose, a somewhat smaller one may be taken next time. The simplest way is to

[1] 'Ueber die Anwendung des Chinin in den fieberhaften Krankheiten des kindlichen Alters,' *Jahrbuch für Kinderheilkunde*, N.F. v., p. 181 et seq. See C. Binz, 'Das Chinin in den Krankheiten des kindlichen Alters,' ibid. vol. i. 1868; G. Mayer, 'Ueber die Anwendung der antipyretischen Methode bei fieberhaften Krankheiten der Kinder,' ibid. vol. vi. 1873, p. 271.

accommodate the largeness of the dose to the particular case. Here we must remember that, as has been already mentioned, in the later stage of the disease the resistance of the fever to the action of the quinine frequently diminishes.

If a diminution of the temperature of the body has been produced by a sufficient dose of quinine, there results usually an abatement also of those fever symptoms which depend on a rise in the temperature.

The pulse rate also as a rule diminishes with the fall of the temperature. In cases in which observations of the temperature and the pulse rate have been made simultaneously, we may frequently satisfy ourselves that the lowering of the pulse rate takes place after the fall of the temperature, so that the former only begins to sink after the latter has already begun to do so; that, moreover, the slowest pulse rate appears as a rule later than the lowest state of the temperature; and that, finally, even the rising again of the pulse rate succeeds that of the temperature. These observations appear to indicate that quinine does not, like many other antipyretic medicines, e.g. digitalis, exercise a direct influence on the heart, or its function, and that the action on the pulse rate appears to be only an indirect one. It becomes slower only because and when the temperature becomes lower; it is with the pulse in the abatement of the fever produced by quinine exactly as it is in abatements otherwise produced, and especially in those which occur spontaneously. Nor is there any fact known to me otherwise to support the assumption that there is a special action of the quinine on the heart and its functions. Yet I would like to call especial attention to this, which indeed is self-evident, that the statements made refer only to the doses employed by me of 20 to 45 grs.; of the action of actual toxic doses I have no experience. Even in cases of advanced weakness of the heart, I have never observed unfavourable effects from the action of quinine; so that even in such cases in which most other antipyretic medicines are contra-indicated, such a contra-indication does not obtain for quinine. Yet in such circumstances special care in the administration is to be recommended. Frequently in such cases, where the temperature of the body is reduced by means of quinine, the pulse rate also becomes diminished.

Yet we may meet with cases with the pulse rate so exceedingly high, that it is not perceptibly affected by the fall in the temperature; and this is of so much more serious prognostic importance, when in such cases, after a spontaneous fall in the temperature, the diminution in the pulse rate is wanting; then it is to be assumed that the weakness of the heart has advanced too far for a return to the normal to be still possible. When a lowering of the pulse rate follows a fall of the temperature, the quality of the pulse usually also improves just as in spontaneous remissions. The frequency of the respiration is also affected by the pulse rate, provided that no other forces are in operation to act upon it in addition to the fever.

Even the other functional disturbances due to a rise in the temperature show a manifest decrease, after a considerable lowering of it by means of quinine. In cases in which under a constantly high temperature serious cerebral symptoms have set in, a considerable abatement of these symptoms is usually observed after a well-marked remission due to the action of quinine. Patients who are in an apathetic condition, or constantly delirious, return to comparatively clear consciousness after the rise in the temperature has ceased, sometimes indeed very soon thereafter, but sometimes only slowly and gradually, just in the same way as usually happens also in spontaneous remissions or such as are otherwise brought about. In many cases tranquil sleep is obtained on abatement of the cerebral symptoms. In most cases also there is a manifest improvement in the general condition; and this improvement usually returns also with the restoration of consciousness. But there are exceptions; patients who were previously apathetic or somnólent, and always, in answer to enquiries, professed to be well, then first became conscious of their sufferings and began to complain when the mind was clear. This symptom, it is well known, appears also in spontaneous resolution of the fever.

On the condition of tissue metamorphosis and the production of heat after the administration of quinine, we possess as yet only sparse and not altogether unambiguous data. Buss (loc. cit. 1878) found the elimination of carbonic acid in fever cases lessened as the result of antipyretic doses of quinine. Even in

the healthy subject he found a small reduction of the elimination of carbonic acid after 15 grains of the drug. Von Boeck and Bauer[1] had found before this, that in animals the production of carbonic acid decreased after the absorption of a small dose of quinine, while very large doses, which gave rise to muscular cramps, produced a considerable increase. It is as yet matter of doubt whether this evidence of a diminution in the elimination of carbonic acid under the influence of quinine is to be referred to the antipyretic action of the drug, and this supplies, perhaps, the first confirmation of the surmise so often hazarded, that the antipyretic act of quinine, possibly of other medicines besides, depends on the diminution of the production of heat. The diminution of the elimination of carbonic acid observed by Buss, followed very soon after the absorption of the quinine, usually before the fall in the temperature of the body had begun, and it even showed itself when, exceptionally, no lowering of the temperature took place. It may be here added, that when salicylic acid was employed, even although the antipyretic action was clearly visible, a diminution of the elimination of carbonic acid was not observed.

The tissue metamorphosis, as it shows itself chiefly in the quantity of urea excreted, was found by Bauer and Künstle[2] not to be diminished in fever cases after an antipyretic dose of quinine, but rather at first somewhat increased. Yet the results of the experiments of these authors, as regards their bearing on what we have stated before (p. 57), may possibly admit of a different explanation. Von Boeck found that in healthy animals the decomposition of the albuminoids was lessened under the influence of quinine.

Salicylic Acid.

As medicine in general was benefited by the discovery of the antiseptic action of salicylic acid, and by the invention of a method suited for its preparation on a large scale (Kolbe), so, by the discovery of the antipyretic action of the acid, has the

[1] 'Ueber den Einfluss einiger Arzneimittel auf den Gasaustausch bei Thieren,' *Zeitschrift für Biologie*, x. 1874, p. 350 et seq.

[2] *Deutsches Archiv für klin. Med.*, vol. xxiv, 1879, p. 63.

number of antipyretic medicines been increased by one of extreme value (Buss). That it does in fact exercise a very distinct antipyretic action, anyone may easily satisfy himself by experiment who sets to work with discretion and some practical knowledge. A serious drawback to the use of the drug, which consisted, on the one hand, in the difficulty with which it dissolves in cold water, and, on the other, in the irritant action which the free acid has on the sensitive mucous membrane, was fortunately overcome by the discovery that its soda salt, which is easily soluble and not locally irritating, exercises the same antipyretic action as the free acid (Moeli, Riess, Buss). Since then the use of the free acid has been everywhere abandoned, and the soda salt, or some other neutral compound, has been adopted instead. When, in what follows, a definite quantity of salicylic acid is mentioned, that quantity of the acid in combination with soda is to be understood.

I am accustomed, partly for the sake of the purity of the preparation, and partly for the greater certainty of the dosage, to use only a freshly made saturated solution, which is extemporised either by the addition of bicarbonate of soda and the necessary dilution with water (mixed with a little aromatic water or brandy), or is prepared by the apothecary according to the following prescription:—

℞ Acid. salicyl. ʒij ss. or 10 grammes.
Sod. carb. q. s. ad perfect. saturat.
Aq. dest.
Aq. menth. pip. aa. ℥iij. or 100 grammes.
Ft. mist.

About 30 grains of salicylic acid may, as regards its antipyretic action, be considered as, on the average, equal to about 15 grs. of quinine (sulphate of quinine). With adults I usually employ, for antipyretic purposes, a dose of salicylate of soda, corresponding to 60 to 90 grs., in the majority of cases to 75 grs., of salicylic acid. For children smaller doses suffice. Thus Hagenbach,[1] for instance, guided by his own experience, fixes the antipyretic dose of salicylate of soda for children under

[1] 'Ueber die Anwendung des Natron salicylicum in fieberhaften Krankheiten des kindlichen Alters,' *Correspondenzblatt für Schweizer. Aerzte*, 1877, No. 15.

a year old at 15 grs., for those from one to five at 20 grs. to 45 grs., and for those from six to fifteen at 50 to 80.

The antipyretic action of salicylic acid is quite as much to be depended on as that of quinine. The extent of the fall in the temperature depends in every case, as it does with quinine, on various special circumstances; and, indeed, in this respect the elements referred to as at work in connection with quinine appear equally active in connection with salicylic acid also, such as the largeness of the dose, the period of the day, the nature and intensity of the disease, its stage, the degree of the obstinacy of the fever in general, the idiosyncrasy of the patient, &c. But even if respect is had beforehand as far as possible to these conditions in the determination of the dose, yet it frequently happens, as in the case of quinine, that the action exceeds the expectation, or comes short of it. The former happens perhaps more frequently with salicylic acid than with quinine. Not unfrequently the temperature falls from 40° or 41° C. (104° to 106° F.) to 37° C. (98·6° F.), or still lower, after an ordinary antipyretic dose of salicylic acid. On the contrary, as with quinine, the temperature of the body, in health or in non-febrile disease, is much less reduced, and sometimes even not at all, by means of a large dose of salicylic acid. In its antipyretic action the symptoms produced by its administration resemble those occurring after the administration of quinine: usually ringing in the ears and sometimes also difficulty of hearing appear; yet these symptoms, where the antipyretic action is the same, are somewhat less prominent than with quinine.

The same indications substantially determine the use of salicylic acid as of quinine. Its action has, it is true, been proved to be much less certain in malarial affections, in which quinine displays not only an antipyretic but a specific action; yet, as regards its special antipyretic action, it has made good its title to be regarded as a perfect substitute in every respect for quinine.

More accurate observation, however, has shown that the action of salicylic acid, even when employed for the purpose of antipyresis, does not entirely correspond with that of quinine; that, in certain respects, variations occur which demand careful attention in the use of it, and somewhat modify the indications for its employment. While referring at the same time to what

I have said on the action of quinine, I shall in what follows principally call attention to the more important points in reference to which the action of salicylic acid has been found to differ from that of quinine. From this it will be easy to deduce the differential indications.

The antipyretic action appears, on the average, considerably sooner after the administration of salicylic acid than of quinine. A definite diminution of the temperature may in general be observed within 1 to 2 hours after the ingestion of a sufficient dose of salicylate of soda, and the greatest diminution happens, on an average, about 4 to 6 hours after its administration. Hence, if we refer the strongest action to the period between midnight and morning, salicylic acid ought to be administered late in the evening, somewhere between 8 and 10. In consequence of the comparatively rapid absorption of the salicylate of soda, it is desirable not to administer the whole dose at one time, but to divide it into small doses and give one of these every hour or hour and a half. By attention to this direction vomiting does not so readily ensue, neither are symptoms of collapse, nor other disagreeable symptoms of its action, so likely to occur. A greater interval between the doses is not to be recommended, because often then the antipyretic action is uncertain. Nevertheless, it is more easy to secure a cumulative action of several successive doses of salicylic acid than of quinine, less, as it seems to me, because the salicylic acid is more slowly eliminated from the blood by the urine than on account of the quicker appearance of the antipyretic action. If we have any doubt, for example, in a particular case, what dose will be required for a satisfactory effect, it is quite proper to administer tentatively at first a somewhat small dose of about 60 grains of salicylic acid. Then, if after some hours the fall in the temperature does not come up to our expectations, we may administer from 30 to 60 grains more, and reckon that the two doses will combine, to some extent, and act together. If we were to administer quinine in a similar manner, we should, in order to be able to judge of the action of the first dose, have usually to wait so long that we could not depend on a sufficiently conjoint action of both doses.

The fall of the temperature due to salicylic acid is accom-

panied in the majority of cases with very profuse perspiration, generally in a much higher degree than after quinine. This is in some measure connected with the fact that, after the administration of salicylic acid, the fall in the temperature usually ensues more rapidly, just as in spontaneously occurring resolution of fever the perspiration is usually more profuse the more quickly the fall takes place. Yet in many cases the impression is conveyed that the salicylic acid possesses a special diaphoretic action as well. This supposition is encouraged by the observation that this secretion of sweat follows the employment of the salicylic acid, while as yet no lowering of the temperature has begun to appear.

The action on the other symptoms dependent on the lowering of the temperature is, in many respects, when the latter is produced by salicylic acid, much the same as when remission of the fever is produced by quinine. Thus the psychical disturbances connected with fever are wont to decrease in a quite similar way. Yet it is to be noticed here that in some cases psychical disturbances and even delirium are induced by salicylic acid. This appears to occur especially when comparatively large doses are being taken for a longer period than ordinary, as in acute articular rheumatism. Where antipyretic doses are administered with long intervals between them, and this occurs, it is because either the patients are remarkably sensitive and excitable or else that one unusually large dose has been very rapidly absorbed. This delirium has generally the character of over-excitement, and is usually easily distinguishable from the delirium of fever.

When a decrease in the temperature has been caused by salicylic acid, a distinct lowering of the pulse rate usually appears as well, and with that the quality of the pulse is generally improved. But we must not disregard the fact that the decrease of the pulse rate is, on the average, less than corresponds with the decrease of the temperature, and less than we should expect with an equal decrease induced spontaneously or by means of quinine. While, in the case of quinine, we are warranted in saying that observations do not support the assumption of a special effect of quinine on the action of the heart, at least with such doses as are administered for the purpose of

antipyresis, facts seem to point to such a special action in the case of salicylic acid. This drug frequently shows in fevers a pulse-accelerating along with a temperature-reducing action, in so far as it prevents the pulse rate from falling to as low a level as corresponds to the temperature. By this means an index is afforded which seems to deserve every attention. Since, in protracted fevers, the termination often depends solely upon this, whether the heart can continue capable of acting or whether higher degrees of cardiac weakness may make their appearance too early, a drug which demonstrably exercises an influence on the heart's action may be regarded as in this respect not unimportant. I used formerly to employ salicylic acid even in cases in which manifest weakness of the heart had already appeared, and sometimes with good results. I have, however, in general entertained the impression that in cases with well-marked cardiac weakness, even when the lowering of the temperature acts favourably, salicylic acid by itself exercises rather an unfavourable action upon the heart. Finally, I have still to add that sometimes after the employment of this drug, especially if the temperature falls quickly on account of excessive perspiration, a certain degree of collapse takes place. In all cases which I have seen, this collapse indeed implied nothing critical, and soon disappeared again, especially if the usual alcoholic stimulants were given. Such a collapse also occurs after the employment of salicylic acid more frequently than after that of quinine, perhaps only because the fall of the temperature usually follows more quickly under it. Guided by present experience, and until we know better (that is, until the somewhat general and indefinite impressions we now have are confirmed or refuted by definite and unequivocal facts), I incline, in all cases in which there are already clear signs of cardiac weakness, to give the preference to quinine over salicylic acid, and in general to regard the presence of that weakness as a contra-indication to the employment of the latter.[1] I discontinue the use of salicylic acid as an antipyretic as soon as the pulse rate becomes unusually high or any signs of considerable decrease of the activity of the heart appear. Where, on

[1] Cf. Goltdammer, 'Zur inneren Anwendung der Salicylsäure,' *Berliner klinische Wochenschrift*, 1876, No. 4.

the contrary, the action of the heart is still strong, and its rate not too high, I regard it as an antipyretic entirely free from danger; and, indeed, I know of no fever which by itself would form a contra-indication to the use of the drug. I have employed it up to the present time in enteric fever, puerperal fever, scarlatina, pneumonia, pleurisy, erysipelas, acute articular rheumatism, endocarditis; finally, also in phthisis and other chronic febrile diseases. In certain diseases the antipyretic action of the salicylic acid appears to be surer than that of quinine, as, for example, in pneumonia, in acute miliary tuberculosis, in many chronic fevers, and, before all, in the disease in which salicylic acid possesses not only an antipyretic but a specific action, viz. in acute rheumatism. I have only further to state that salicylic acid and quinine by no means exclude each other, but may be administered to the same patient, either after one another, or combined in such a way that their actions as regards time coincide and are conjoined.[1]

The elimination of carbonic acid was found by Buss (loc. cit. 1878, p. 67 et seq.) not to be lessened in fevers after the employment of salicylic acid, even after a distinct lowering of the temperature had already set in.

According to the investigations of Wolfsohn,[2] which he conducted under the direction of Jaffé, the excretion of urea is increased in the case of dogs under the action of salicylic acid. Bauer and Künstle[3] likewise infer from their experiments in fever cases an increase in the decomposition of albuminoids in consequence of the action of salicylic acid.

Digitalis.

Though digitalis had previously been extensively employed in febrile diseases, and especially in pneumonia, as an empiric remedy, Traube (loc. cit.) was the first to prove by means of experiment that it exercised an important antipyretic action in pneumonia and other inflammatory fevers. Ever since

[1] See A. E. Burckhardt, 'Beiträge zur Kenntniss der Basler Typhusepidemie von 1877,' p. 17. Dissertation. Basel, 1878.

[2] *Jahresbericht von Virchow und Hirsch*, 1876, i. pp. 193, 420.

[3] *Deutsches Archiv für klin. Med.*, vol. xxiv. 1879.

Wunderlich (loc. cit.) employed and recommended this drug in enteric fever, and other observers (Thomas, Ferber) tried it also in the same disease, it has come to be regarded as a general antipyretic.

Digitalis is most frequently used in the form of the infusion, and this form also deserves the preference in many cases of heart disease; but if it is used as an antipyretic, the administration of the leaves themselves, in powder or in pill, is much to be preferred, on the one hand, because in these forms the action is much surer, and, on the other, because the necessary dose can be more easily introduced within a definite time. The total dose to be taken is considerably lower when it is thus administered than when the far less active infusion is employed. I am in the habit of using from 10 to 20 grains in 24 to 36 hours. While with quinine and salicylic acid, which are excreted again in a comparatively short time through the urine, the total dose must be taken in the shortest possible time, this is not necessary with digitalis; here cumulative action takes place, and the total dose may be spread over one or even several days, and yet its action be manifest. The antipyretic action, however, is always quicker and surer when the dose is not spread over too many days. If, in specially severe and obstinate fevers, a sufficient reduction of the temperature cannot be effected by means of quinine, the desired effect, I find, may be secured by means of the combined action of digitalis and quinine. I prescribe 10 to 25 grains of digitalis in the course of from 24 to 36 hours, and give immediately thereafter a full dose of quinine (30 to 45 grains). If we are once successful in interrupting in this way the obstinacy of the fever, and in effecting a complete intermission, then we frequently succeed afterwards by means of quinine alone.

The antipyretic action of digitalis by itself is less certain than that of quinine. It is comparatively slow in its operation, but it has a somewhat longer duration. The proper dosage is in some degree difficult to fix, since different individuals show a different amount of sensibility to the action of the drug, and because it is sometimes more, at other times less effective. This difficulty is best overcome by spreading the dose over a certain period, in the way already mentioned, and by suspending

administration of it as soon as distinct symptoms of its action show themselves. Many of these symptoms, such as dryness and harshness in the throat, a feeling of sickness, and even vomiting, have no really injurious effect; but the further administration of the drug must be stopped with the appearance of these, and especially of vomiting. Digitalis, on the other hand, has an important effect on the action of the heart, and the circumstance that it exercises in a comparatively direct way, viz. without an intermediate effect upon the temperature of the body, an influence upon the heart's action, must of necessity lead to a certain restriction of the indications for its use in fever.

In non-febrile cases the rate of the pulse is usually lowered by means of digitalis. Its surprisingly favourable effect in many cases of imperfect cardiac action, with a considerably increased pulse rate, is due to this, that the pulsations of the heart become stronger along with the lessening of their frequency. Thus we see in patients, in whom the action of the heart is imperfect, and on account of which dropsy and other results of a retarded systemic circulation have arisen, that all the symptoms of obstructed circulation often disappear comparatively quickly under the use of digitalis. Agreeably to the analogy of this action in non-febrile diseases with that in cardiac debility, we might be tempted to employ digitalis in preference to other remedies also in fevers where symptoms of cardiac weakness exist. And it has, in fact, frequently been recommended as an antipyretic, especially in those cases in which the pulse rate is unusually high. But this statement of the indication, so long as it is not established by direct observation, is by no means to be accepted as correct till we know more about the matter. In non-febrile cases it also happens that when the enfeeblement of the heart is too far advanced digitalis does not succeed, as then it seems to act unfavourably upon the heart, and to foster the appearance of paralysis of that organ. Experience shows us that this is the rule in fevers with an unusually high pulse rate, so long as the fever continues high. In previous years I repeatedly tried the employment of digitalis in cases of fever accompanied with weakness of the heart, but in no case did I succeed in strengthening the heart's action by

that means, or even in lowering the excessively high pulse rate. I had the impression rather as if in particular cases the weakness of the heart was still further increased by means of it, and the occurrence of cardiac paralysis favoured. If, on the other hand, in the later stages of the disease, the fever has ceased or considerably decreased, but the weakness of the heart and the unusually high pulse rate still continue, then we may not unfrequently succeed in bringing about improvement by its use. The same indications are then met with as in patients without fever.

After such experience I have decided to confine the use of digitalis as an antipyretic to those cases in which the pulse rate is not yet unusually high, and in which no pronounced symptoms of weakness of the heart as yet exist. In such cases —for example, in the commencement of an attack of pneumonia, or even of one of enteric fever—the use of this drug in antipyretic doses is perfectly safe. We may say then in general that, though varying in some degree from its indications in diseases of the heart, digitalis appears to be the less indicated as an antipyretic the higher the pulse rate is. Since we have in salicylic acid an antipyretic of very prompt action, which—even in cases where quinine does not suffice—either by itself or in combination with quinine, generally enables us to secure the action we wish for, I have in acute fevers only rarely had occasion to make use of the antipyretic action of digitalis.

Digitalis has in particular circumstances the advantage over quinine in chronic fevers; and, although at variance with an opinion still extensively prevailing, which is supported only by imperfect analogy, the indications may admit of being formulated in the following way: The more the fever is of the nature of a continued fever the more is quinine the proper agent to employ for the production of artificial intermissions; the more the fever is remittent or intermittent the more is digitalis indicated. In hectic fever, as it occurs in pulmonary phthisis, for example, if antipyretic medicines in general appear to be indicated, I am in the habit of employing both medicines combined, so that pulv. fol. digital., $1\frac{1}{2}$ to 3 grains, and sulphate of quinine, 7 to 15 grains per diem, are made up in the form of pills. A distinct decrease of fever usually ensues very soon. The chief

action in this case is, no doubt, to be ascribed to the digitalis, the more that the decrease of the fever frequently coincides with the commencement of other effects of digitalis (such as decrease of the pulse rate, a sense of dryness and harshness in the throat, sickness, and tendency to vomit). In direct experiments made with digitalis alone, the action did not appear, however, to be so favourable as when the combination with quinine was employed; and hence I have reverted to the latter prescription.

Veratrine.

Although veratrine had been already employed as an empiric or specific remedy in different febrile diseases, especially in pneumonia (Aran, 1853), and in acute articular rheumatism, it was first discovered to be an effective antipyretic by M. Vogt (loc. cit. 1859) on the ground of his observations on enteric fever, pneumonia, and acute articular rheumatism. It was afterwards employed as such by other physicians also, especially in pneumonia; and in particular we may refer to the accurate communications of Kocher (loc. cit.), which were made in Biemer's clinic at Berne, on the results of the treatment of pneumonia with veratrine and other preparations of veratrum.

Formerly I used veratrine as an antipyretic, especially in enteric fever, but in other febrile diseases also, though more rarely, and by means of it I often obtained satisfactory remissions, and even complete intermissions, in cases in which quinine did not act to my satisfaction. I prescribed it usually in the form of pills, which contained 0·075 grain of veratrine each, and one every hour until severe sickness or vomiting set in. Usually 4 to 6 pills sufficed.

After the employment of veratrine the pulse rate, if it was not previously very high, usually becomes considerably lower, and this decrease is not, as under quinine, effected by means of a lowering of the temperature. We may not unfrequently feel satisfied rather that the decrease of the pulse rate appears sooner than the lowering of the temperature. We must, therefore, assume that the veratrine acts more directly upon the functions of the heart, as is the case also with digitalis. Collapse takes place more easily under veratrine than under the other anti-

pyretic remedies as yet described, especially if vomiting sets in and the diminution of the temperature follows very quickly. In the cases in which I have observed this, the collapse never proved serious, and was soon overcome by means of wine or other analeptics. I have used the drug only for patients in whom the cardiac action was still pretty strong, and I consider in general that pronounced symptoms of weakness of the heart contra-indicate the use of veratrine still more so than that of salicylic acid and digitalis. In recent years I have given up the use of veratrine, since the possible indication for its employment may be met usually with more certainty and less discomfort by means of salicylic acid.

Alcoholics.

Towards the end of the last century, at the time of the prevalence of the Brownian theory, strong alcoholic liquors in large doses were in frequent use, and were employed on a large scale in fevers, and particularly in severe asthenic forms of fever, without any regard being had to their action on the temperature of the body. In recent times alcohol has been frequently employed in fever, in comparatively large doses, especially in England, and indeed, as appears, with good results, or at any rate without any harm. In Germany, on the other hand, the majority of physicians are of opinion that the employment of alcoholics in severe fever is dangerous, because they exercise a heating action, and are calculated therefore to intensify the fever. The subjective sense of heat and the rise in the pulse rate, as these usually appear after the employment of these remedies, seem to support this view.

My attention was long ago called to certain isolated statements of observers which seemed to indicate that the action of alcohol on the bodily temperature in health might possibly be quite a different thing from what was usually supposed. These were, irrespective of the earlier observations of Prout, especially the investigations of Vierordt,[1] and of the assiduous though one-sided Böcker,[2] the founder of the more recent theory of

[1] *Physiologie des Athmens*, p. 92 et seq., p. 244. Karlsruhe, 1845.

[2] *Beiträge zur Heilkunde, insbesondere zur Krankheits-, Genussmittel- und Arzneiwirkungslehre*, vol. i., 'Genussmittel,' p. 249 et seq. Crefeld, 1849.

stimulants. In 1859 I became convinced by experiments on myself that by the use of alcoholic liquors a rise in the temperature of the body was never produced, but usually a slight reduction rather. And control experiments showed that this decrease was greater and also of longer continuance than usually happened after the absorption of equal quantities of water of the same temperature. The lowest temperature which I ever observed on myself (35·8° C. [96·5° F.] in the axilla) occurred at night, after I had, for the purpose of experiment, drank in the evening a bottle of strong red wine (medoc). Since that time I have, without hesitation, extensively employed wine and other alcoholics in fevers, and have never seen a rise in the temperature from their use, such as might have been inferred.

The question as to the action of alcoholics on the temperature of the body has been revived during the last ten years, within which period observations on it have appeared from several quarters, of which those of Binz and Bouvier (loc. cit.) are to be particularly mentioned. These observers have shown that the temperature of the body is not raised by the administration of alcoholics in the case of men and animals, whether in health or disease, but is frequently lowered in a marked degree. Later observations of Binz and his pupils, as well as of other investigators, among whom we may particularly mention Marvaud,[1] Riegel,[2] Strassburg,[3] Daub,[4] L. Lewin,[5] have in substance confirmed this statement.

In such non-toxic doses as may be used in fevers, alcohol induces only a slight reduction of the temperature of the body, and we should never think of employing it, as we do quinine, salicylic acid, digitalis, and veratrine, in continuously high fever, in order to insure considerable remissions or complete intermissions. But the other antipyretic treatment employed

[1] *Les Aliments d'Epargne*, 2nd edit. p. 232. Paris, 1874.

[2] 'Ueber den Einfluss des Alkohols auf die Körperwärme,' *Deutsches Archiv für klin. Med.*, vol. xii. 1874, p. 79.

[3] 'Experimenteller Beitrag zur Wirkung des Alkohols im Fieber,' *Virchow's Archiv*, vol. lx. 1874, p. 471.

[4] 'Ueber die Wirkung des Weingeistes auf die Körperwärme,' *Archiv für experimentelle Pathologie*, vol. iii. 1875, p. 260.

[5] 'Ueber die Verwerthung des Alkohols in fieberhaften Krankheiten,' *Deutsches Archiv für klin. Med.*, vol. xvi. 1875, p. 564.

may be effectively aided by the use of it.[1] The real indications for the use of alcohol in fever belong to another province. It is in particular an important dietetic remedy, and it is also a very effective analeptic. The great importance of the most recent investigations on the effects of alcohol is due to this: that by means of them it has been proved with certainty that the fear lest the temperature of the body should be increased still more by the use of alcoholics is groundless, and that, by the removal of this, the most serious scruple as to its use in fevers has been finally set aside. Alcoholics will yet be extensively employed in fevers, much less, however, as remedies directed against the fever or against the rise in the temperature than for the meeting of other extremely important and frequently recurring indications.

Other Antipyretic Medicines.[2]

Besides the drugs already treated of there is a great number of others in which antipyretic actions have been either proved to exist or may with some reason be presumed to exist, and probably the number of these will soon be considerably increased. It is possible that some of these drugs, when once their mode of action has been empirically established by extended observations on fever patients, may be proved to be suitable for adoption as antipyretic remedies. Of none of them, however, are we able as yet to say that the investigations regarding them are such as to warrant us in placing them on the same level as quinine, salicylic acid, digitalis, or veratrine. The mere evidence that the temperature of the body is reduced after the employment of a drug in any strong dose, in the case of animals or of healthy subjects, or even of fever patients, is by no means enough to justify us in pronouncing it a useful antipyretic. In this respect it is enough to remember that, with most poisons, when they are administered in toxic doses, the temperature of the body is usually reduced before the fatal symptoms appear. A reduction of the temperature of the body, such as is induced

[1] Cf. *Mittheilungen aus der Klinik von Breisky*, Berne; F. Conrad, *Ueber Alkohol- und Chininbehandlung bei Puerperalfieber*' Berne, 1875.

[2] For notices of some recent antipyretic remedies *vide* end of volume.

by a weakening of all the vital functions, is not antipyresis, but the commencement of death. Nevertheless, when we find that a drug, along with its other toxic actions, causes also a remarkable lowering of the temperature of the body, this may be regarded as an index inviting us to further investigations of its physiological action, especially with reference to the question of its action on the temperature of the body. And in this sense many remedies may find a place in the following list, which, if they are administered in sufficient doses, may indeed cause a lowering of the temperature of the body, but which are not at all likely to prove to be useful antipyretics. And finally, some more remedies may be named which have not yet been shown to possess a temperature-reducing action, but which seem to deserve to be tested in this respect more thoroughly than they have been. I may mention further that I have myself never used one of these drugs as an antipyretic in man with the exception of some derivatives of quinine, and that I have therefore no personal experience of their action. Of some of them, when employed to meet other indications (as calomel in enteric fever, tartar emetic and other emetics), I have been able also to prove their temperature-reducing action.

The other alkaloids of cinchona bark and their derivatives may be classed alongside of quinine. The preparation which is sold under the name of quinoidine I long ago frequently tried as an antipyretic, but I had soon to give it up, because vomiting usually set in when I attempted to administer a sufficient dose of it. Cinchonine and, according to more recent investigations (Strümpell), also quinidine are especially to be mentioned. On account of a certain similarity of action we may perhaps also here include preparations of eucalyptus, piperine, beberine, berberine, and some other organic bases.

In the salicylic acid group we may perhaps include salicin (Senator), creosotic acid (Buss), thymol (Bälz), carbolic acid, benzoic acid, picric acid, as well as numerous other substances that are chemically or physiologically related.

Closely allied to veratrine, as regards action, are some other constituents of the veratrum group, and perhaps also aconitine, colchicine, &c. Morphine, physostigmine, pilocarpine, nicotine, curara, and prussic acid may be also mentioned here.

With ethylic alcohol may be closely connected some other alcohols, as also several simple and compound ethers, finally chloroform and perhaps hydrate of chloral. From volatile oils also, and especially from camphor (Binz), a lowering of the temperature of the body is to be expected, when they are administered in large doses.

After the administration of calomel in large doses in enteric fever, there generally follows a transient lowering of the temperature, a result to which both Traube and Wunderlich have already called attention, and which I can confirm from my own observation. The lowering of the temperature under the influence of tartar emetic, which appears along with symptoms of weakness of the heart (Ackermann), is perhaps to be considered as, in part, a symptom of collapse. Also other purgatives and emetics seem, when given in massive doses, to induce a lowering of the temperature.

Here we may also include preparations of arsenic and iodine, as well as the salts of potassium, and finally acids, the mineral acids as well as, and perhaps preferably, the organic acids.

APPENDIX—Blood-letting.

In addition to what we have said in regard to antipyretic medicines, reference may here also be made to blood-letting, in so far as by means of it an antipyretic action can be brought about. Galen, even in his time, had recourse to venesection until faintness was induced, as the surest means for lowering the rise of temperature due to fever; and he expressly lays stress on blood-letting and cold as the two greatest remedies in continued fever.[1] Marshall Hall,[2] by means of experiments with determinations of temperature on healthy dogs, has proved that a considerable lowering of the temperature takes place if blood-letting is continued until syncope ensues. He advised that the patient should be made to sit up during the operation, as in that case fainting, which is to be regarded as the limit for the blood-letting, appears sooner. Later observers have always found a lowering in the temperature of the body

[1] Galeni *Methodus medendi*, ix. 4; ed. Kühn, x. p. 612. Id. ix. 5; ed. Kühn, x. p. 624.

[2] *On Blood-letting.*

as a result of blood-letting in fevers, when there was a large enough withdrawal of blood. Even those physicians who but seldom employ blood-letting, have frequently occasion to observe the action of a great loss of blood on the temperature of the body in cases of fever. After serious intestinal hæmorrhages in enteric fever, or after abortion with very great loss of blood, or even after unusually profuse bleeding from the nose, I have repeatedly seen the temperature, which had previously risen above 40° C., fall one degree or more, or even return to the normal. With the decrease of the fever the disturbances due to the rise in the temperature also decrease in like manner as in other considerable remissions. The lessening or disappearance of the cerebral symptoms is frequently very striking, and the pulse rate also may show a decrease. In most cases, however, more or less complete collapse takes place at the same time as a consequence of the loss of blood. And the favourable action of this loss is, moreover, only temporary: usually the temperature begins to rise again before 24 hours have elapsed, and the disease resumes its ordinary course; only the power of the patient to resist the rise in the temperature is immensely diminished in consequence of the loss of blood, and the danger of paralysis of the heart is much increased.

There is therefore no doubt that a febrile increase of temperature may be quickly reduced by means of a sufficient blood-letting, and, until very recently, a specially high degree of fever was looked on as among the indications for the need of blood-letting. But, since the danger is materially increased by the loss of blood as regards the further course of the disease, especially in cases in which a long duration of the fever is to be looked for, and since we have also other remedies by means of which we can reduce the temperature of the body as certainly and as quickly, there is the less occasion to resort to blood-letting as an antipyretic remedy. The indications for this are to be sought for in another direction.

CHAPTER III.

ANTIPYRETIC DIETETICS.

Hippokrates: Περὶ διαίτης ὀξέων. Ed. Kühn, ii. p. 25. Ed. Ermerins, i. p. 287.—F. A. G. Berndt: 'Die Fieberlehre,' part i. p. 140 et seq. Leipzig, 1830.—F. W. Böcker: *Beiträge zur Heilkunde, insbesondere zur Krankheits-, Genussmittel- und Arzneiwirkungs-Lehre.* Vol. i. 'Genussmittel.' Crefeld, 1849.—L. Stromeyer: 'Ueber die Behandlung des Typhus.' 2nd edit. Hanover, 1870.—J. Wiel: 'Diätetisches Kochbuch.' 2nd edit. Freiburg i. Br., 1873.—A. Marvaud: 'Les Aliments d'Epargne, Alcool et Boissons Aromatiques (Café, Thé, Maté, Cacao, Coca).' 2nd edit. Paris, 1874.—J. Uffelmann: 'Die Diät in den acut-fieberhaften Krankheiten.' Leipzig, 1877.—C. E. Buss: 'Ueber Wesen und Behandlung des Fiebers.' Stuttgart, 1878. Vide the numerous works of M. von Pettenkofer and C. Voit on the physiological significance of the various foods in 'Zeitschrift für Biologie.'

The somewhat energetic antipyretic methods already spoken of, if they are to be attended with success in cases of fever, are recommended on the presumption that the whole dietetic arrangements made for the patient are suitably regulated, and that in these circumstances all influences calculated to increase the fever are as much as possible avoided. Where this condition is not complied with, the most carefully conducted and energetic antipyresis will often yield no favourable result; while, on the other hand, there are numerous individual cases of fever in which a proper dietetic treatment is by itself sufficient, and all energetic antipyretic measures may be dispensed with.

The antipyretic system of dieting has first of all a negative task. Among the influences which usually accompany fever it has to single out those that are to be avoided as much as possible, because they tend to increase the fever. But it has also positively to specify how the necessary conditions for the sup-

port of the patient are to be regulated, in order to make the chances as favourable as possible for a moderate course of the fever and a favourable resolution of it. Antipyretic dietetics must aim, on the one hand, at rendering the production of heat as inconsiderable, and at keeping the temperature of the body as low, as possible, and, on the other, at maintaining as much as may be the patient's capability of resistance.

The importance of suitable diet in cases of fever is evident from this fact, among other things, that it affects in many cases the course and issue of the disease, whether the patient comes soon or late under treatment. And this appears not only where under particular circumstances an energetic antipyretic treatment is employed by means of heat abstraction or of antipyretic medicines, but it is still more clearly apparent where, while only the so called expectant treatment is being employed, great stress is laid on proper dieting in the widest sense.

We shall, in what follows, treat of the more important dietetic measures so far as they refer to fever as such, without entering upon the modifications which may be required in connection with the special peculiarities of different febrile diseases.

Bodily and Mental Rest.

In healthy men the production of carbonic acid and of heat is, as we know, increased in a very high degree by muscular exertion, so as under certain circumstances, such as very great exertion, to amount to many times the normal production;[1] in this case the temperature of the body is also increased, as the increase in the loss of heat does not keep pace with that of its production.[2] Muscular exertion produces the same effect in fever, and hence it follows, as one of the most important rules of a fever dietary, that the utmost rest possible is one of the most urgent necessities for such patients. There are patients, as there are physicians even still, who believe that it is proper

[1] *Handbuch der Pathologie und Therapie des Fiebers*, p. 190 et seq. Leipzig, 1875.

[2] Ibid. p. 80 et seq.

to contend as long and vigorously as possible against the disease, and not to go to bed until the physical impossibility of sitting up renders it necessary. Observation proves that by such a line of action the condition of the patient is rendered worse. I have seen patients who were suffering from simple typhus (*typhus levis*) or influenza, who sought to resist the attack with all their might and often by means of bodily exertion, sink in such a surprising way that I was at first forced to suspect the presence of some other serious disease, it might be pulmonary phthisis, or in other cases carcinoma of the stomach, or the like, and the convalescence was protracted to such an extent as never happens otherwise in such mild cases.[1] The fatal effects of bodily exertion and fatigue in severe fever cases I had especial occasion to observe in the typhous patients connected with the army of Bourbaki, quartered in Switzerland, whose symptoms were those of the severest type of the disease, and many of whom died in the first few days after their arrival, while in the case of the rest its further course showed that the disease in itself was not at all of particular intensity. It was observed by several physicians during the war, that even a too long railway journey is extraordinarily exhausting for typhous patients, and renders their condition, for a time at least, very much worse.[2]

Every patient suffering from fever, whether the case is one of acute or chronic disease, ought to be in bed; only in apparently quite slight cases, such as catarrhal fever or subacute quinsey, &c., ought an exception to be made in some circumstances, and the patient allowed to spend part of the day in a recumbent posture on the sofa. In chronic cases also, when accompanied with hectic fever, constant rest in bed is to be urgently recommended. In phthisical patients, who suffer from chronic fever, all remedies employed against the fever are usually without effect so long as the patient refuses to submit to absolute rest. On the other hand, if the patient only steadily keeps to his bed, the fever is often seen to abate

[1] Cf. such a case observed by me and reported in the *Prager Vierteljahrschrift*, vol. lxxxvii. p. 71.

[2] See observations on this subject by F. Niemeyer, *Deutsches Archiv für klin. Med.*, vol. viii. pp. 435, 443.

or altogether disappear, even under otherwise indifferent treatment. It is only, at most, when in the morning hours the temperature keeps within the normal limits, and the evening exacerbation is inconsiderable, that the patient is to be allowed to get up for an hour or two in the morning, and he must be careful to return to bed before the febrile exacerbation sets in again.

After diseases in any degree serious the first attempt to get up is permissible at the very soonest only when the temperature in the evening has been found to be perfectly normal for several days. The first attempts, too, must only be of short continuance, and the first stage of convalescence must be completed chiefly in bed. Apart from the fact that getting up too early frequently induces reactionary fever, and that in individual cases this may give rise to actual relapse, experience also shows that the patient recovers far more rapidly and regains his full strength much sooner when he spends the greatest portion of the convalescent period in bed.

Finally, it is of the utmost importance strictly to prohibit all mental activity, and especially the accustomed mental occupation, to forbid every attempt to read or to be read to, to withhold all reports on matters of business, everything that might excite, and the like; loud noises and too much light are to be guarded against.

We may here refer to the observations of W. Manasseïn,[1] which appear to show that passive movements under certain circumstances may be attended with a temperature-reducing effect. This observer found that the temperature of the body of rabbits may with certainty be reduced by swinging them to and fro, and that this was the case with healthy animals as well as with those in which a rise in the temperature had been induced by putrid injection. It is worthy of remark that passive movements were had recourse to in ancient times to counteract fever. Thus Celsus[2] relates that Asclepiades recommended them as a means of subduing fever, even in acute and violent cases, and especially in *febris ardens*. Celsus, however, considers rest safer in such cases. Along with other kinds of passive

[1] 'Zur Lehre von den temperaturherabsetzenden Mitteln,' *Pflüger's Archiv für Physiologie*, iv. 1871, p. 283.

[2] Celsus, ii. 15.

movement, he instances this very swinging motion. Either the bed is to be hung up, he says, or, if that is not practicable, one foot of the bedstead at least may be raised on a block, and the bed then swayed to and fro.

The Sick Chamber and its Hygiene.

In hospitals it is important, more particularly for fever patients, that the wards should not be too large, and that, in proportion to their cubic contents, they should contain as few patients as possible. In badly conducted hospitals, in which only certain wards are provided with the necessary requisites for the convenient use of baths and the like, it is customary for those suffering from fever to be crowded together in these rooms by preference. This proceeding is not calculated to promote the object contemplated. Regard for the patients, as well as for those in attendance, must lead to the distribution of as many of the fever patients as possible among the other patients. Obviously we do not mean to include the directly contagious diseases, such as smallpox, measles, scarlatina, and typhus, which must be isolated with the utmost strictness, each class by itself. On the contrary, with patients suffering, for example, from enteric fever, pneumonia, &c., it is better if they are distributed among the others. All the larger wards in a hospital should possess a supply of cold and warm water; and where this is not the case, it is much to be desired that the defect should be remedied. It will then be no longer necessary to select the room according to the treatment which each patient may require, or to change it afterwards in the course of the disease. Baths are best given close beside the bed of the patient by pushing the bath, which must be provided with castors, up to the bed. To transport the patient, as has been recommended, out of the sick chamber into a bath-room provided for the purpose is a proceeding not to be approved of, on account of the disagreeable psychical impression it is apt to produce. And where the hospital arrangements are to any extent satisfactory, the preparation of the bath in the ward is so simple that no other patient need be disturbed by it.

In private practice a roomy chamber should be selected for

the patient, removed as far as possible from all noise. The bed should be so placed that the light may not shine direct on the patient's face. To many patients a moderate softening down of the daylight is grateful. Only one person should, as a rule, remain in the room to take charge of the patient. All conversation with him should be avoided; only necessary questions should be answered. At the same time, all the wants of the patient should be attended to as noiselessly as possible, even those which he himself does not express. It adds to the comfort if a room adjoining is given up exclusively for the benefit of the nursing arrangements.

For a patient who gets baths, one bed is usually enough, provided that on the whole he only rarely soils it, and that there is time enough during the bath to change the bedclothes as often as necessary, and to arrange the bed again. If, on the other hand, there are no baths, or none any longer necessary, it is very advisable that there should be two beds at the service of the patient, that he may have a change. In that case, however, he must not walk over from one bed to the other, but he must be carried in a horizontal position; or, if the beds are close together, he may at most slide over from one to the other. It is of great importance, in tedious cases in which there is reason to fear bed-sores, that the mattresses be firm and yet yielding, and that the sheets be always kept smooth. The laying of patients on large water cushions is also to be highly recommended. The sufficient employment of antipyretics contributes, indeed, very greatly to the prevention of bed-sores.

The evacuation of stools and urine must, in severe cases, always be made in a recumbent position, the bed-pan and urine-glass being pushed underneath. Many patients insist at first that they are able to make their stools only in a sitting position, but even these generally soon get accustomed to defæcation when lying down.

The temperature of the sick room should be a little lower than the usual temperature of sitting-rooms; it should never be for any time under 14° C. (57° F.), and never over 18° C. (64° F.) Attention should be paid to the necessary change of air by day and night. It is very desirable, as Stromeyer (loc. cit.) recommends, that in hospitals there should be an opening

in the lower part of the door of the room, and that several of the panes in the windows should be made to open. Every kind of complicated ventilating apparatus is much to be encouraged, but not if simple ventilation by openings in the windows and doors is to be in consequence neglected. In private houses, where it is at all possible, a window in the adjoining room should be kept constantly more or less open, even in winter, and the door between the two apartments should always stand open. Even a strong draught of air, if transient, is quite harmless in fever. Exposing patients constantly to this draught, or lowering the temperature of the room so much that the patient constantly shivers, is not to be thought of; especially since the stronger heat abstractions are not to be superseded by such means.

The determinations of temperature are least annoying to the patient when they are made in the rectum; and patients who are aware that their case is a critical one do not usually object to the proceeding. The experience of recent years has satisfied me that the determinations of temperature in the rectum may be entrusted to competent and conscientious female nurses, even in the case of male patients. Only if the rectum become sensitive to its continuance, or if—as rarely happens in mild cases—other things have to be taken into consideration, should the temperature be determined in the axilla. The determinations of temperature taken by the nurse in the axilla frequently show too low a value; in the rectum the numbers read off, if a division of the mercurial column has by chance taken place, may, on the other hand, be much too high. We may with certainty conclude that we have to do with a surprisingly high temperature if we can see the gradual rise of the quicksilver after the introduction of the thermometer, or its gradual fall while the instrument is being slowly withdrawn.

Diet.

On the important question, What is the nourishment proper for fever patients? widely different opinions prevailed in former times. There is no doubt the idea that the patient ought not to receive any nourishment, because by that means the fever might be nourished at the same time, was in former times

frequently carried too far, and English physicians in particular deserve credit for having called attention to the evils connected with too great abstinence, and for pointing out that suitable food is useful and necessary, even though the patient declares he has no need of any. On the other hand, however, there is just as little doubt that in over-estimating the waste which takes place in fever, and the danger connected with it, matters were carried to an extravagant length when the best possible nourishment was prescribed for patients suffering from serious fever, and large quantities of flesh were attempted to be given to them. In recent times a gratifying unanimity in regard to the more important points may be shown to exist among authors who have studied the subject of the nourishment of fever patients.

A final decision of the question, What is the proper quantity, and especially what is the proper kind, of nourishment for fever patients? will be arrived at only when, on the one hand, we rightly combine the results of our enquiries on the nature and the dangers of fever with the results of investigations on the physiological importance of individual food stuffs, and when, on the other hand, we go on experimenting, and along with our own observations maintain a due regard to the results of experience obtained at the sick bed for the past thousand years. In this we shall have to distinguish between acute and chronic febrile diseases.

In *acute diseases* a very considerable waste of the constituents of the body takes place in consequence of the fever, and it is therefore certainly desirable to repair the loss as much as possible. But our former discussions (p. 4 et seq.) have shown that the danger to which the patient is exposed is not so much due to this waste as to the rise in the temperature of the body. In acute fevers, therefore, the increase of the temperature demands the strictest attention, and the repair of the waste is of only subordinate importance. Direct experience, too, shows that in severe fever cases of short duration deficiency in the nourishment causes no material injury to the patient. The longer, however, the fever lasts, and the more the course of the disease approaches the chronic type, the more the question of nourishment is gradually brought into the foreground.

Even in *chronic febrile diseases* the rise in the temperature,

both in itself and its influence on the system, is, it is true, of great importance, and certainly accounts materially for the capacity of resistance of the organism so often giving way sooner than it would do under mere waste without a rise at the same time in the temperature. It is but seldom, however, that the amount and duration of the increase in the temperature gives rise to immediate and sudden danger, while, on the other hand, the gradual waste of the constituents of the body really in the end causes death by exhaustion. We should therefore in chronic febrile disorders pay special attention to the indication for nourishing the patient as well as possible, but in doing so we should see that the quantity and the quality of the nourishment always correspond with the condition of the fever at the time, and that the temperature of the body is not increased anew by an unsuitable regimen.

Diet in Acute Disease.

All physicians in more modern times agree in regard to one article of food, viz. that, at least, an equal quantity of water is as necessary in disease as in health. In regard to this we must remember that the healthy man, besides the quantity of water which he takes in the form of different kinds of liquids, absorbs also a considerable quantity in the so called solid food which he consumes. Such fever patients even as are in a state of tolerably clear consciousness, unless they are expressly required to do so, are frequently indisposed to take the necessary quantity of liquid. When the fever is in any degree severe, the patient should therefore have, when he is not sleeping, the glass or the spoon applied to his lips every quarter or every half hour. It has often been noticed that after that he willingly drinks, although he is still far from calling for liquid or stretching out his hand to the glass. If, however, he expressly refuses the draught when offered him, we should desist from pressing him. He should moreover be allowed to drink only a small quantity at once. In giving him liquid we should remember that the colder it is the more another indication for treatment, viz. heat abstraction, is met, though only to a small extent. The nature of the drink must be regulated according

to the taste of the patient, and it may be changed as often as he wishes. The drinks to be recommended are simple cold water, with or without pieces of ice, sugar water, natural seltzer water or other similar mineral waters, wine and water, lemonades made with lemon, vinegar, tartaric acid, or mineral acids, mixed or not with a little sugar, fruit juice, or syrup; also thin milk of almonds (*Mandelmilch*), thin decoction of slightly roasted rice, thin barley water, milk and water, coffee, tea, &c.

Amongst foods in the stricter sense we shall have to make such a selection as, while paying all respect to the experience we already possess of the physiological importance of individual foodstuffs in general, to give the preference to those respecting which we know that by employing them tissue metamorphosis and the production of heat, and especially also the waste of the tissues, are not increased but rather diminished. Besides this, however, we must remember that, as experience proves, the functions of the stomach and the intestinal canal are seriously impaired during fever, and that all kinds of food which are not digested and absorbed are injurious, that abnormal decompositions may occur, gastric and intestinal catarrh be provoked, and the fever increased. By considerations such as these, the selection from the food stuffs at our disposal is materially restricted.

The employment of *albuminoids* in any considerable quantity is forbidden by the consideration, that patients suffering from severe fever would not be able to digest them in the form in which they are usually partaken of by people in health; and besides, from all that we know of their physiological action, an excess of them in the food would rather lead us to expect a general increase of the tissue metamorphosis. Also as regards *fats*, experience teaches that when given in too great quantity they are not digested or, at any rate, absorbed during the fever. *Carbo-hydrates*, on the other hand, are digested and absorbed without difficulty if they are taken in a proper form; and, as regards their physiological action, we know that although they cannot really contribute to the formation of tissue, as they undergo oxidation relatively quickly and completely, yet their employment causes a general decrease of tissue metamorphosis, and in particular a material saving in fats and albuminoids. In

this last respect two other substances rank close to the carbo-hydrates, one of which in particular is to be reckoned as belonging rather to luxuries than to food stuffs in the strictest sense. These are gelatin and alcohol.

We are thus led, as the result of practical experience and theoretical considerations, to assign the foremost place to carbo-hydrates of all the different food stuffs employed in the nourishment of fever patients. Obviously, however, it were a theoretic extravagance if anyone were therefore to think of giving a patient carbo-hydrates exclusively and of trying to nourish him with starchy food, sugar, or honey. Not to speak of the aversion which such a mode of nourishment would soon excite on account of its monotony, an appropriate mixture of different food stuffs is a necessary condition in a dietary in any way satisfactory. What should be done, therefore, is to select from the different kinds of food at our disposal those which can, on the one hand, be digested and absorbed by patients suffering from fever, and which, on the other, contain the different food stuffs so admixed as to be suitable for his use. In severe fevers, solid food usually remains undigested, and is therefore to be avoided. Everything administered should be in a fluid state, or else the solid constituents of it should be finely divided. And such food must always be administered in small quantities at a time, while, on the other hand, it must be given at short intervals, yet not without some attention to the previous habits of the patient in reference to the time of his principal meals. As regards their composition, those kinds of food deserve the preference which contain albuminoids and fats only in small quantities, while they at the same time abound in carbo-hydrates.

If we regulate the nourishment according to these views, we arrive substantially at that fever diet which experienced physicians of all times have been in the habit of recommending ever since the days of Hippocrates, and from which only a physician here and there has deviated who suffered himself to be guided in his prescriptions more by the theoretic opinions temporarily prevailing than by actual experience at the bedside. There still remains ample scope for the regulation of the diet in individual cases. For example, in determining the kind of nourishment, we ought to take into account the inclinations

and habits of the patient, and, as far as practicable, even the changing likes and dislikes, and, in regard to quantity as well as kind, also the nature of the disease, the direct implication or comparative freedom of the digestive organs, the present state of the appetite, of the tongue, and of the whole intestinal tract; but before all, the duration and the stage of the disease. In diseases which last but a short time, too great abstinence does no harm; and this is especially the case when, in the beginning of severe febrile diseases, although we give the requisite quantity of water, we administer to the patient only a moderate quantity of food. The more, however, the disease is protracted, the more carefully must attention be paid to a liberal repair of the waste.

For patients suffering from serious fevers we may recommend, for example, decoctions of certain grains, using for these either the whole grain, or the meal, of barley, oats, rice, of which only the thin part (gruel) and not the solid residue is used. The decoction may be made with the addition of beef or some substance that yields gelatin. We may even add extract of meat in moderate quantity, by means of which the soluble salts of the beef are in a desirable way introduced into the system; for the extract is only of importance otherwise as being agreeable to the palate. Too great quantities of the extract of meat serve no purpose, and are injurious rather than otherwise; the superstitious belief that it is a specially concentrated form of nourishment, and of about equal value to meat, no longer stands in need of any refutation in medical circles. Decoctions of fresh and dried fruit are desirable in certain circumstances, and barley, sago, and the like may also be added to them. Milk may also be given if the patient does not dislike it and is able to bear it, but only after it has been boiled, and in many cases diluted with water, seltzer water, weak tea, coffee, fennel tea, &c. Even extract of malt in a convenient vehicle may be employed; and to many foods in a fluid state sugar, and particularly grape sugar, may be added with propriety. The longer the illness lasts the oftener the yolk of an egg should be beaten up in the beef tea or the barley water. In the later stage of the disease concentrated beef tea, made by boiling the meat for a long time in a closed vessel, or, better still, in a

Papin's pot, is advisable, or even Leube's preparations of meat; also Liebig's beef tea, prepared by maceration of the meat in the cold with dilute hydrochloric acid, and mixed with red wine; also, according to Voit and Bauer, freshly expressed meat juice, and, finally, the usual peptones.

In spite of the many theoretic doubts which exist in regard to its importance as a food, gelatin has always kept its place in the economy of the kitchen, and in the form of so called jelly soup and potted meat it has been held in the highest repute, even in the sick chamber. In many districts there is for patients a preference for barley water prepared with a decoction of calf's foot or other substances abounding in tissues that yield gelatin; and among the older physicians decoctions with hartshorn were very much used in fever cases (see, e.g., Berndt, loc. cit. p. 145). Even in very recent times weakly acidulated gelatinous foods have been recommended by Wiel (loc. cit. p. 214) as an agreeable change for fever patients, and that on merely empirical grounds, unconnected with theory. The employment of gelatin has also been theoretically indicated very lately by the investigations of Voit, who believes it to be a food which, like the carbo-hydrates, and even in a still higher degree than they, results in a saving of the albumen. On the ground of these investigations gelatin has been repeatedly recommended as a nutritive substance in fevers.[1]

Wine and other alcoholics are allowable at every stage, and especially at the very height of the fever (see p. 92). By the investigations of Binz and his pupils it has been proved[2] that by far the greatest part of the alcohol is oxidised in the organism, and that to it, therefore, besides its stimulating action, a certain nutritive value is also to be ascribed. Its importance as an article of diet in fever cases is still further enhanced by this, that we may by means of it, as the older and also the more recent investigations already mentioned seem to show, look for a general diminution of the tissue metamorphosis, and therefore the preservation of the body from too rapid waste. The different

[1] H. Senator, *Untersuchungen über den fieberhaften Process und seine Behandlung*, p. 184 et seq., Berlin, 1873; J. Uffelmann, l.c. p. 81.

[2] C. Binz, 'Die Ausscheidung des Weingeistes durch Nieren und Lungen,' *Archiv für experimentelle Pathologie*, vol. vi. 1877, p. 287.

alcoholic beverages in use, and wine in particular, may be administered unmixed, as well as also diluted with water, and even mixed with many other of the drinks mentioned above, or with food in a liquid form. As regards the form and quantity, we ought to be guided by the previous habits of the patient. If a patient has been accustomed when in health to the regular use of alcohol it should not be denied him during fever. Beyond this I consider it unsuitable to press unusually large doses of alcohol upon a patient prematurely when there is no special indication requiring it. We ought rather to remember that in the further course of the disease a strongly stimulant action may possibly be necessary at a particular stage, and that we ought then to be still able to increase the quantity sufficiently for such a purpose.

In less acute fevers, we may, if the digestive apparatus is in a comparatively efficient state, carry our attempts at nourishment a little further with impunity, and add a somewhat greater quantity of albumen in convenient form to the food. The nourishment should also, though with caution, be increased in severe cases as soon as, along with the abatement of the fever, the condition of the digestive organs begins to improve. This rule, as Buss (loc. cit. p. 211 et seq.) in particular insists, holds good also for intercurrent fevers, and especially too for artificially produced remissions and intermissions, which may quite conveniently be used for supplying to the patient a somewhat more liberal nourishment. Irrespective of every other advantage, a judicious antipyresis is of importance also on this account, that by means of it we shall be the sooner able to give the patient better nourishment, especially if, in the way to be described hereafter, our efforts are directed as much as possible to the production of strong remissions, or approximately complete intermissions. The greatest caution, however, is always to be observed, and the state of the digestive organs at the time must be carefully enquired into, and we may in general maintain that in severe acute diseases an unseasonable overloading of the stomach with food will generally result in greater injury than an abstinence which may perhaps go a little beyond what is absolutely required.

Solid foods, such as meat and bread, may be given only

when the patient is steadily free from fever, and even then we should remember the possibility of a relapse, or, under certain circumstances, even serious harm resulting from this if the necessary caution is not observed as regards quantity. Frequently great harm is done by those in attendance on the patient by pressing him to take a too great quantity of food, from the wish to restore his strength as soon as possible. As long as he has no decided appetite the patient should not be pressed with food. It is enough to place something suitable beside him, and should he decline it, it is certainly better for him not to take it. On the contrary, if in convalescence the appetite is very active, it is often necessary not to gratify it to the full. Small and often repeated meals are in general to be preferred.

In the writings of Hippocrates on diet in acute diseases, and especially in the one referred to above, the greatest importance is attached to the right use of ptisane, a decoction of whole barley; and a careful distinction is drawn between the cases in which simple ptisane is to be used and those in which it has to be administered mixed with the residue. Besides this, mixtures of honey and water (μελίκρητον), and of honey, water, and vinegar (ὀξύμελι), and finally different kinds of wine were used as drinks. In ancient times, drinks prepared from millet seed, flour, and grain of wheat were also employed.[1]

On the whole, in spite of all changes as to theory, and in spite of various differences in individual cases, the diet for fever patients has continued much the same up to our own times; and this fact is a certain guarantee that the principle at bottom is in substance correct.

Serviceable recipes for the preparation of different kinds of food for fever patients are given, among others, by Berndt (loc. cit. p. 143).

According to Stromeyer (loc. cit.), the best food for a typhus patient is oatmeal, which should be boiled for three hours and not be mixed with sugar.

The salivary and buccal secretions are considerably diminished, as a rule, in fever. According to the investigations of

[1] See also Haeser, *Geschichte der Medicin*, 3rd edit. vol. i. p. 161. Jena, 1874.

Uffelmann, expressly undertaken to decide this point (loc. cit. p. 32), the power of these secretions, which is always present in moderate fever, to convert starch into sugar is sometimes wanting in high fever, and in very high fever, and especially in continuously adynamic states, is almost always extinguished. The less abundant the secretion is, and the less we can reckon on its maintaining its amylolytic power, the more is a supply of starchy food in any quantity to be avoided. On the other hand we may in such cases venture to employ grape sugar, of which it is to be assumed that it will be sure to be absorbed and utilised by the tissues.

The experiment of Buss (loc. cit. p. 217 et seq.), which he made on patients suffering from long-continued serious febrile diseases, of conveying considerable quantities of food in a form in which it did not require to be digested, appears to be well worthy of notice. In a great number of typhus patients, who were fed in this way with comparatively large quantities of grape sugar and peptones, and that, too, chiefly during the spontaneous or artificial remissions of the fever, the diminution in the weight of the body was during the course of the disease considerably less than it usually is under the ordinary kind of nourishment.

Raw eggs used to be regarded by the laity as a food specially easy of absorption, while in reality they appear to task the power of digestion more than the boiled white or yolk of the egg when finely divided. In severe fevers they are entirely unsuitable.

Many stimulants, such as coffee, tea, cocoa, appear to lessen the metamorphosis of tissue, and especially of the albuminoids (see Böcker, loc. cit. i. p. 118 et seq.; Marvaud, loc. cit. p. 292 et seq.) Experience teaches us that we need not hesitate to employ them in fevers in moderate quantities.

Diet in Chronic Fever.

Among the dangers of fever, in chronic febrile diseases, febrile waste so decisively comes to the front that the question of sufficient diet becomes one of pre-eminent importance. In numerous instances of such chronic cases the course and issue

of the disease depend on this more than on anything else—whether the waste will go on steadily increasing, or whether we can succeed in checking it and keeping the patient up to the same condition of nutrition as previously, or in even effecting a decided improvement in that condition. In many cases we may in the most convincing manner satisfy ourselves that, by means of a material improvement in the condition of nutrition, the patient is not only kept up longer, but that the fever also is moderated and a fresh exacerbation of it prevented.

So long as in chronic diseases the fever continues of any severity, and makes only small and transient remissions, the same principles in substance are to be adhered to in the selection of food as in the later stages of an acute fever. We must take every care and see that as much food is absorbed as the condition of the stomach and the intestines admits of, but we must be equally careful not to overstep the limits prescribed by the capability of the digestive apparatus.

If the fever decreases, or makes stronger remissions or intermissions, we may go further in regard to food, and still more if from time to time there appear longer periods with no fever or with only very little. In chronic diseases it is of the utmost importance that these periods be utilised as diligently as possible for the improvement of nutrition.

The principles which determine the selection of the food are deducible from what we know of the several food stuffs. These principles may be grasped by us in a simple and practical way if we reflect on the action of the so called Banting diet. From this it at once appears that the foods which are rich in albuminoids are not those by which waste is lessened; and we must therefore order an anti-Banting diet. The prescription of the physician should aim at this, that as much fats and carbo-hydrates as possible may be consumed. The use of albuminoids may be left to the inclination and taste of the patient, after we have warned him not to fancy that he will succeed in regaining his strength by a free indulgence in beefsteaks and eggs.

Milk is the best food for patients suffering from chronic fever. Where the fever is not violent, milk is usually easily borne if the patient is slowly and regularly accustomed to it,

while he goes on gradually increasing the quantity at a definitely prescribed rate. It is important that we should see that, while only moderate quantities are to be taken at a time, the allowance should be frequently repeated. Boiled milk is much to be preferred to unboiled, partly because there is the unquestionable possibility of injurious substances being in certain circumstances introduced when the milk is unboiled, and, on the other hand and chiefly, because, as experience shows, unboiled milk in large quantities usually soon induces dislike to it. If a patient takes every day from 3 to $4\frac{1}{2}$ pints of milk, we may allow him, if he still has appetite for more, to gratify it to the full, according to his taste and inclination, but always with the reserve that fats and carbohydrates are more to be recommended than large quantities of albuminoids, that, therefore, for example, if the patient likes it, bread-and-butter is better than meat and eggs. Some white bread may sometimes be taken with advantage in the milk, and the latter may also be administered with a little rice meal, &c., added to the usual milk food. If a patient shows a dislike to milk, it is best to discontinue it entirely for 8 to 14 days, and then to begin with it again.

Among fats, *cod-liver oil* may be most easily absorbed in sufficient quantity. If our intention is to exercise by means of it a real influence on nutrition, it is desirable that we should administer about 35 ounces per week; and by beginning with a spoonful morning and evening, and slowly increasing the quantity, the patient may often so take to it that he will learn at length to consume every morning and evening from 5 to 6 spoonfuls, which will then be taken of course no more with a spoon, but all at once, and best out of a glass previously moistened with some cherry brandy. If after some months the regular continuance of this should prove disagreeable, we may very well exchange the milk treatment for the cod-liver oil, and *vice versa*, or else we may employ the two together, each in a correspondingly smaller quantity.

When neither milk nor cod-liver oil is well borne in sufficient quantity, there is little hope that we will succeed in bringing about some material improvement in the nutritive condition; and it is often advisable to explain this to the

patient; for many a one, who might think himself unable to take the milk or the oil, learns to do so very well when he is convinced that this is the only way to insure his improvement or recovery. We may always venture to employ substitutes, yet we must never forget that as great results are only to be expected when corresponding quantities are absorbed. Thus, for instance, instead of cod-liver oil, even butter may be employed, or any other fatty substance, at discretion; but only few patients will bear sufficient quantities of these for a long time.

The same is true of the carbo-hydrates, which may be used as substitutes for the fats. Thus, for example, the extract of malt, so much recommended, is hardly ever consumed in such quantities as to lead us to expect a perceptible influence on nutrition from it. On the other hand the grape cure, if large quantities of grapes are consumed and borne, may serve at times as a substitute for milk or cod-liver oil. Finally, we must remember that the southern wines, which abound in alcohol and sugar, if they are taken in large quantities, possess a not inconsiderable nutritious value. Where a single remedy is not borne in the quantity that is to be desired, then we may sometimes succeed in accomplishing something by proper combinations.

The use of alcoholics is without risk in chronic fevers also, and they are to be recommended, especially in the form of strong wine or strong beer. They do not, in general, in large quantities go well with the milk cure, since they often impair the appetite or the ability to absorb the milk; on the other hand, they can be combined well with the cod-liver oil cure, or with the more commonly mixed diet. Infusions also of coffee, tea, and cocoa may be permitted, provided they are not taken hot. They seem, like the alcoholics, to lessen in some degree the general tissue metamorphosis; and by their use the milk cure may be rendered more agreeable to many persons.

The question has sometimes been raised, whether we should therefore be justified in chronic diseases in directing our therapeutics before all to the improvement of the state of nutrition; whether, for example, it would be a benefit to a patient suffering from pulmonary phthisis if we were to exert ourselves

to increase the weight of the body, or, perhaps, even to make him store up a good deal of fat without paying much attention to the affection of the lungs; whether in such a case, it is not much more rational, on the one hand, to treat that affection directly, and, on the other, to contend with the fever that perhaps accompanies it by means of effective antipyretic remedies. As regards such questions we will not deny that an effective specific or local treatment of pulmonary phthisis is much more to be desired than any indirect treatment. We are ready even to admit that the endeavour to find out a specific treatment for this disease is perfectly legitimate, and if we even entertain no great hopes, and are in particular far from ascribing importance to every theoretically constructed cure so long as it is not sufficiently practically tested, yet we have till now no reason to despair of the possibility that such a specific may one day be found. But so long as we know of no effective specific treatment, and quite as little of a thoroughly efficient local treatment, we must attach great importance to the indirect general treatment. And as respects this we can only appeal to the results of experience. Now, this teaches us that, in very many local processes of disease, the best possible nourishment of the patient is of importance, not only because by means of it an arrest of the waste is made, but because, through the actual state of the nutrition, the condition and the course of the local disease are effectively influenced. Experienced surgeons, under certain circumstances, in the case of purely local affections, when these happen to be inaccessible to local treatment, or offer an obstinate resistance to such, are in the habit of selecting the indirect course, and of acting on the local disease by doing what they can to improve the general nutrition. I know cases, for example, in which various processes, that for years defied all local treatment, were permanently healed by means of a long-continued cure with large doses of cod-liver oil. In diseases of the internal organs, it very often happens that we must relinquish a direct local treatment, but if we succeed in putting the patient into a better nutritive condition, or even in effecting a considerable accumulation of fat, we see even pulmonary consumption in the majority of cases take a more favourable course. In general,

in numerous local diseases, whether accompanied by fever or not, the best treatment is to begin by increasing the weight of the patient by means of proper nourishment. And in many chronic diseases accompanied by fever we have a much greater prospect of securing a reduction, and in the end a lasting cessation of the fever, by carefully enjoining an antipyretic dietary in the widest sense than by trusting to antipyretic medicines or other energetic antipyretic measures.

CHAPTER IV.

APPLICATION OF ANTIPYRESIS, AND ITS RESULTS.

After explaining in the preceding chapters the several remedies and methods by means of which we may be able to reduce the rise in the temperature of the body due to fever, we shall in what follows have still to explain under what circumstances the employment of antipyretic remedies is enjoined, and in what way these are to be used. As regards this, misunderstandings and mistakes have not unfrequently occurred.

There are physicians who have fancied that what the antipyretic treatment has to do is to suppress the fever completely, or to do so, at any rate, as far as possible; that it has, for example, to make every effort to keep a patient with typhoid at a normal or nearly normal temperature during the whole course of the disease, and in particular to cut short at once every exacerbation of the fever. It also happens, and that especially with physicians who only occasionally take the temperature of their patients, that they are alarmed if they once find a temperature of more than 40° C. (104° F.); they then fancy that there is some pressing danger to life, and that all the antipyretic methods of treatment must immediately be called into action. Much more frequently still is the opposite the case, that, while an antipyretic treatment of the fever patient is resolved upon, a hesitation is felt in employing thorough measures; where a cold bath is indicated, a tepid one is used; where frequent baths are necessary, only single ones are employed; where a large dose of quinine should be administered, only a small dose is given, &c. It is not always easy to find the proper mean, which, by avoiding both extremes, brings about the result at which we are aiming; and we shall be in some degree in a condition to secure this only when we seek to form to ourselves as

clear ideas as possible, on the one hand, in regard to the object to be aimed at, and, on the other, in regard to the remedy to be applied and its bearings in the case.

It is more easy to remove another misunderstanding. In the antipyretic methods of cure we have referred to a series of energetically active measures and remedies. Now, some even very intelligent and well-meaning physicians have supposed that every fever patient is treated by us with innumerable baths and enormous doses of quinine, digitalis, veratrine, and other strong drugs. On this supposition they have thought themselves bound to raise their voices and utter a protest against the employment of antipyretic methods.[1] This supposition is obviously grounded on a mistake. When a surgeon writes a text book on operative surgery, in which are described all the serious operations which may under particular circumstances be necessary, no one therefore fancies that the author would adopt all these in the case of any single patient that may come into his hands. As respects this, we may be permitted to refer to the statements which follow as to the frequency with which the several antipyretic remedies are to be used.

Indications for Antipyresis.

Every fever patient requires an antipyretic system of diet that shall be appropriate to his own case; but energetic antipyretic measures or medicines are not necessary with all fever patients. Among the different febrile diseases in which the use of such energetic measures is not indicated we must first of all mention those in which, as regards the fever, the *indicatio causalis* can be met. To this class belong many cases of symptomatic fever, such, for example, as happens in suppurations. We may under certain circumstances succeed, by means of an operation, in removing the source from which the fever proceeds, and therewith allay the fever also; while in other cases a suitable local treatment may be a prior condition to an effective treatment of the fever. To the diseases accom-

[1] Vide W. T. Gairdner, 'The Antipyretic Treatment of Specific Fevers,' *Glasgow Medical Journal*, Sept. 1878; Liebermeister, 'On the Antipyretic Treatment in Specific Fevers,' a letter to Prof. Gairdner, ibid., November.

panied with fever in which a special antipyretic treatment is generally unnecessary, belong all those which admit of an effective specific treatment. We ordinarily treat neither ague nor acute articular rheumatism antipyretically; on the contrary, in the one disease we employ quinine and, in the other, salicylic acid as specifics, and expect that when the specific action appears the fever will cease. And if for typhoid as also pneumonia, scarlatina, and other febrile diseases, similar effective specific methods of treatment should once be found—which certainly, from the theoretic views now prevailing and our experience hitherto, we can by no means regard as an altogether vain hope—we should welcome the discovery with great satisfaction, and never hesitate a moment to give the preference to these specifics over the antipyretic treatment. Neither in more remote nor in more recent times have there been wanting doctrinaire explanations and theoretical proposals in this direction, and these views have been very lately again propounded by the defenders of the parasitic theory of disease. Unfortunately, however, the search after specific remedies—for the legitimacy of which, as a matter of principle, we have moreover argued with all heartiness already[1]—has not yet led to any practical results; and so, until we arrive at something better, we are glad to possess in antipyresis, if not a specific and radical, yet an effective, symptomatic remedy, by means of which the lives of many patients may be saved who would otherwise succumb to the intensity of the fever. We know, indeed, that the serious acute diseases come to an end even without any help from us; and we must not regard therapeutics as impotent even though, when rightly appreciating the limits of their capability, we restrict their use to merely taking care that the patient does not sink under the disease.

A certain specific action belongs, in enteric fever, to calomel as formerly administered in large doses, in so far as by means of it the course of the fever is in many cases rendered easier and shorter. But this specific action is only a limited one;

[1] *Deutsches Archiv für klinische Medicin*, vol. iv. 1868, p. 421; art. 'Typhus abdominalis' in Ziemssen's *Handbuch der speciellen Pathologie und Therapie*, vol. ii. 1, p. 204, Leipzig, 1874; 2nd edit. 1876, p. 206; *Handbuch der Pathologie und Therapie des Fiebers*, p. 581, Leipzig, 1875.

many cases maintain in spite of it a severe and long course (loc. cit.) Whether salicylic acid has a specific action in enteric fever, as has been maintained by Riess, on the ground of his experience,[1] and as has very recently been rendered probable by Immermann, so far at least as concerns the prevention of relapses,[2] I cannot determine from my own experience. From the employment, however, of the remedy in a case that has already broken out, and in doses that are to be regarded as admissible, there is usually no specific action discernible by virtue of which antipyresis would be rendered superfluous.

Prophylaxis is on principle of still greater importance in many diseases than their specific treatment. Perhaps we may venture to hope that proper hygienic measures will contribute to render many serious febrile diseases much less frequent, and thus to limit in a most rational way the province of the antipyretic treatment.

Even in those febrile diseases which do not as yet admit of an effective specific treatment, an energetic antipyretic proceeding is by no means indicated in every case. This is only required in those cases in which, in consequence of the fever, real danger is imminent. A slight rise in the temperature is comparatively free from danger; but with the height of the temperature the danger of the patient increases at a rapid rate. This knowledge should lead us at once to seek for the indications for combating the fever every time the temperature reaches or exceeds a certain degree; and upon this is grounded the rule formerly mentioned, which was almost universally accepted at the first on the introduction of the thorough treatment by means of cold baths, that a heat-abstraction is always necessary when the temperature reaches or exceeds 39° C. (102·2° F.) in the axilla, or 39·5° C. (103·1° F.) in the rectum. This rule has proved itself good in practice as a standard one, and it may, under certain circumstances, even now, be still used as such.

But it is not only the degree of the fever that is deter-

[1] L. Riess, 'Ueber die innerliche Anwendung der Salicylsäure,' *Berl. klin. Wochenschrift*, 1875, Nos. 50, 51.

[2] H. Immermann, 'Ueber die Prophylaxe von Typhusrecidiven,' *Correspondenzblatt für Schweizer Aerzte*, 1878, Nos. 23, 24.

minative. If in a catarrhal fever or a catarrhal tonsilitis the temperature rises to 40° C. (104° F.) or more, no active interference is necessary on that account. We can foresee that even without treatment the temperature will soon fall again. In a fit of ague, in which the temperature rose as high as 42° C., (107·6° F.), I let the rise of temperature go on without interference, although afterwards, however, I took care by administering quinine to prevent the recurrence of such a severe attack. A high temperature is dangerous only when it lasts any time, and, in the diseases referred to, a too long continuance of it is not to be expected.

In febrile diseases of longer duration, an active antipyretic treatment is recommended only when the temperature remains high continuously, or when, in consequence of the time it lasts, danger from febrile waste begins to show itself. Many slight and moderately severe cases of enteric fever, many cases of typical pneumonia, of erysipelas, of measles, &c., do not require any active antipyretic treatment. In order to decide whether such a course is necessary or unnecessary, very many factors have to be taken into account, as, for example, the course of the temperature that has been previously noticed in the patient, the nature of the disease, and the further progress of it that we have reason to expect, judging from other experiences. The individual characteristics of the patient are of pre-eminent importance, and require careful consideration. In the case, for example, of an old or feeble man, of a drunkard, of a man with emphysema, of a woman in a pregnant or in a puerperal condition, we must reckon a temperature as fraught with danger and requiring vigorous treatment which in many other persons would cause us no anxiety. In some cases also we find ourselves obliged to have recourse to sharp treatment, the more if signs appear that the rise in the temperature hitherto has not been altogether unattended with injurious results. It is not always easy to come to a decision in this matter. It may happen, for example, that a case of enteric fever, the commencement of which led us to expect a gentle or an abortive course, nevertheless develops into a long, protracted, and dangerous case. Even in a case of pneumonia or of erysipelas it is impossible to foresee how many aggravations may set

in, and how long thereafter the fever will last. And finally, there are cases in which the diagnosis is uncertain at the commencement. In all doubtful cases, a prudent physician will prefer the more certain method to that which is less so, and rather adopt at once an antipyretic course without any urgent necessity than, by neglect of the treatment at the right time, imperil the life of the patient. Cold baths can never do any harm to a patient with a high temperature of the body (see p. 59), even though the later course of the disease should perhaps show that they were not absolutely necessary. If in the case of a child, for example, the temperature has risen quickly above 40° C. (104° F.), and the physician, in anticipation of something serious, employs immediately a cold bath, he may be sure that he does no harm by means of it, even though the disease should next day turn out to be only an ephemeral fever. On the whole, it cannot be often enough repeated and strongly enough insisted on that in this department of therapeutics sins of omission are much worse than those of commission. The antipyretic treatment cannot pretend to repair the damage which has been already done by means of a high and too long protracted rise of the temperature. It can only undertake to guard against such harm. This task is to be completely accomplished only when measures are taken at the right time—that is, before the rise in the temperature has had the effect of irreparably injuring any important organs. And I may be also allowed to remark here, that, though frequently made, it is a bad excuse when a physician, in regard to a patient who after a too long duration of a severe fever rapidly succumbs from paralysis of the heart, tries to justify his expectant treatment by pleading that up to that time no threatening symptoms had shown themselves, and that therefore no indications for energetic measures were present. If he had observed and considered the temperature, and had he been acquainted with the danger of a sustained rise in the temperature, he might have foreseen the danger and prevented it.

Application of the Antipyretic Treatment.

In order to determine more exactly in what way antipyretic agents should be employed, it is of importance to keep this fact in mind, that all our antipyretic remedies, even the most effective of them, produce only a temporary and limited effect; that in every case, even those in which we have been completely successful in lowering the temperature of the body to the desired extent, if the spontaneous resolution of the fever has not meanwhile appeared, the temperature soon begins to rise again, and will in a longer or shorter time attain to its original height. With all our remedies, therefore, we can only produce an effect for a certain time, and a permanent removal of the fever is only to be expected when we are prepared to employ again and again strong antipyretic measures in quick succession. There is room, however, to conclude *a priori* that such an energetic treatment, even when it is sufficient to suppress the fever entirely, would in many cases be attended with serious injury to the patient. Experience also shows that a proceeding so violent as this is not necessary, but that we may, on the contrary, set the antipyretic treatment to perform a task far more gentle, and therefore more easy of application.

It has been already repeatedly insisted on, that the danger from the fever does not only depend on the absolute height of the temperature, but that, what is of decided importance, is rather the length of time during which the temperature continues at this height. A fever which, though very high, lasts only a short time is in general borne better than a fever of longer continuance but with a lower temperature. Even the absolutely fatal degrees of temperature, i.e. of 42° C. (107·6° F.) and upwards, may be borne for a very short time without any evil consequences. In a case of traumatic erysipelas, I once saw the temperature in the rectum rise as high as 42·5° C. (108·5° F.), but it soon sank again, and the patient suffered no material damage from the temporary excessive rise of the temperature.

Many universally admitted facts, which might otherwise perhaps appear surprising, admit of a simple explanation if we

take into account the length of time during which the rise in the temperature continues. Thus we see that recurrent fever, in which a condition of continued fever lasts a shorter time, is less dangerous, in spite of the higher average degrees of temperature, than enteric fever, in which the fever usually lasts far longer. In our ordinary intermittent malarial fevers, in which during the paroxysms the temperature often rises above 41° C. (105·8° F.), and in individual cases even as far as 42° C. (107·6° F.), there is no real danger from the fever. The high degrees of temperature are only of short duration, and during the intermissions the patient, as well as the several organs of his body, may recover again, and the injuries that have perhaps been sustained may be repaired. Hectic fever, which during the daily exacerbation exceeds 40° C. (104° F.), is indeed very serious on account of the great febrile waste connected with it, but there is no sudden danger in consequence of the rise in the temperature by itself; the patient bears such a fever for a comparatively long time without any appearance of cardiac or cerebral paralysis, and if the fever should in the end cease before the waste has gone too far, he may then recover from its effects completely.

On the other hand, the danger of a rise in the temperature is very great when it continues high without intermission. A continued fever in which the temperature is constantly above 40° C. (104° F.) is by its very continuance fatal even to the strongest individuals. And in severe cases of enteric fever, typhus, pneumonia, scarlatina, &c., the fever is so dangerous only because the temperature usually continues for a long time at a great height without any material abatement.

The experiences referred to show us a way by which we may succeed in diminishing or in removing the danger of continued fever without requiring to have recourse to violent and, in another direction, serious measures. As experience teaches, an intermission of any duration in the fever is sufficient to rectify the disturbances caused by a temporary rise in the temperature, or at least so far that they do no great permanent damage, and that even a recurrence of the rise in the temperature, if it does not last too long, is borne without danger to the life of the patient. If we could change every continued fever into an

intermittent fever, the danger from the high temperature in acute diseases would in the main be removed. From this it immediately follows that in acute diseases the indication for the antipyretic treatment is the less urgent the more the fever is spontaneously remittent or intermittent, and the more urgent the more the fever is a continued one. And in continued fever we do not need to try and suppress the fever completely: it is enough for the removal of the danger, if we succeed in bringing about strong remissions or intermissions for any length of time.

A knowledge of this is of great practical importance, because by means of it we aim at an actually attainable object. By a proper application of antipyretic methods we usually succeed in effecting sufficient remissions even in obstinate continued fever. If, on the other hand, we should choose to aim at a complete removal of the fever, we would not in severe cases usually attain this object, or only do so to the injury of the patient.

In assigning to the antipyretic treatment merely the task of changing the continued fever in severe diseases into a strongly remittent one, we express a view in opposition to that of numerous physicians who, while they adopt in like manner antipyretic treatment, yet consider that its duty is to suppress the fever where that is possible, but at all events all stronger exacerbations of it, and to limit it as much as possible to a uniform comparatively low temperature. In this, however, the majority find that their object is not to be attained by means of the remedies which can be employed without hesitation; and those, who are bent nevertheless upon attaining their end by strong measures, have in some circumstances made matters much worse. In this respect the results which the thorough carrying out of antipyresis by means of salicylic acid has yielded are very instructive. Riess[1] employed it on patients with enteric fever in such a way that, as often as the temperature was above 39° C. (102·2° F.), a dose of usually 75 grains of salicylic acid was administered, generally neutralised by carbonate of soda, or in solution along with phosphate of soda. The temperature was taken every 2 hours, day and night. In exceptionally

[1] 'Ueber die innerliche Anwendung der Salicylsäure,' *Berliner klinische Wochenschrift*, 1875, Nos. 50, 51.

obstinate cases cold baths were also employed at the same time. By this means the temperature was constantly kept throughout the whole course of the disease comparatively low. This observer appears to believe that, by employing the drug in this way, he has succeeded in proving that it has a specific action tending to shorten the period of the disease. But the final result was, that, of 260 cases of typhoid, 63 died—that there was consequently a mortality of 24·2 per cent. Though we must agree with the author in the opinion which he expresses that, under all circumstances, the percentages of mortality are not alone decisive in regard to the value of a method of treatment, yet there is no doubt that a method which gives in enteric fever a mortality of 24 per cent. is not to be recommended.

Accordingly, so long as we do not possess trustworthy remedies by which we may directly remove the disease we may be sure of this—that, when it has taken its course, the fever, in typhoid, scarlatina, pneumonia, erysipelas, &c., will cease of itself; we should therefore limit the antipyretic treatment to observing accurately the fever and its effects on the patient during the course of the disease, and to bringing about artificial remissions as often as is necessary to avert the danger arising from the fever. It is impossible to lay down a general rule as to how often such remissions should be brought about. For that purpose the special conditions present in each individual case have to be taken into consideration; besides this, the nature and course of the disease and, before all, the idiosyncrasies of the patient, require to be carefully attended to. Not infrequently, even when we have limited our task in this way, we shall be unable to accomplish all we may perhaps deem desirable, but be obliged to content ourselves with what is actually attainable.

Choice of Time.

What we have advanced hitherto in regard to the scope of antipyresis, is manifestly not in accordance with the notion that what we have chiefly to remember in the antipyretic treatment is to guard against too high degrees of temperature, and therefore, before all, to interfere at the time of the exacerbation or to prevent its onset. If we wish to make a breach in a fortress, we do not select the very strongest part as the point of attack,

but, on the contrary, are careful to seek out the weakest. If our object is to bring about strong remissions, we ought not to choose for that purpose the time when the temperature is on the point of rising, and therefore very obstinately resists every attempt made to reduce it, but the time when it is on the point of falling, and can by antipyretic measures be easily reduced both more quickly and more thoroughly. We ought to use our measures at the time of the exacerbation only when exceptional circumstances require it, such as, e.g., a temperature so high as to threaten immediate danger, or else some particular condition of the patient which may make us feel that any further rise may be very serious. But we usually let the exacerbation run its course without interference, for we know that even high degrees of temperature are attended with no real danger if they do not last long. On the contrary, we seek to concentrate the whole antipyretic action as much as possible on the time of the spontaneous remission, and to stake everything on deepening and prolonging this, and thus making the dangerous type of continued fever as much as possible similar to that of intermittent fever, which is free from danger. The greatest spontaneous reduction of the temperature usually occurs in the night time, and especially between midnight and morning. This time accordingly is the best for bringing about artificial remissions; and that time must therefore be selected for the antipyretic action when it may be expected to produce the greatest effect. Cold baths, in which the greatest action appears soon after their use, are therefore to be given preferably in the night time, and particularly after midnight. As regards quinine, since its greatest action usually appears on the average 8 to 12 hours after it has been taken, we have already specified the time between 3 and 7 o'clock in the afternoon as the most favourable for administering it. As regards salicylic acid, the action of which appears considerably sooner, the best opportunity for administering it is in the late hours of the evening.

These statements in regard to the choice of the time are in complete accordance with the experience we have already communicated in regard to the diversity in the extent of the action of antipyretic remedies at the different hours of the day. As

regards cold baths, it appears from a wide range of statistics that their action, as it shows itself in the state of the temperature of the body about two hours afterwards, is at its maximum during the night, and especially at the time from midnight till morning (p. 38 et seq.); and in a still more striking manner comparative estimates in regard to the action of quinine have shown, that the lowering of the temperature due to it is very much greater in the morning than in the evening hours, and that this diversity appears in some measure independent of the time of administering it. In regard to the action of other antipyretics, we do not yet possess such a range of observations as is necessary to construct reliable statistics.

The conception of the indications, as it has been explained above, commends itself also on the ground that there no longer exists any theoretic objection which otherwise, and perhaps not altogether unjustly, might be brought against the employment of antipyretics. As already stated (p. 3), the older physicians held the opinion that fever was to be looked on as the result of an effort of nature to recover health. They fancied that the body rid itself of the materials of the disease by means of the fever, and that therefore the fever was necessary in order to the recovery of the patient. This assumption of a depurative action of fever, which had gradually formed and developed itself more definitely in the post-Galenic period, was shared in by all physicians until the most recent times; and, however diverse the scientific and practical ideas on other matters, and particularly the conception of fever in individual cases, might be, it constituted the real groundwork for the theory of fever and its treatment. It is only recently that such theories have been discountenanced, and that principally on account of the teleological mode of regarding the matter, which seemed to be incompatible with the more modern tendency of scientific enquiry. But this older view has not been contradicted by facts; on the contrary, many facts brought to light in recent times are in harmony with it, and the views in regard to the etiology and pathogenesis of fever, as these have gradually developed in the two last decades, must be accepted as directly in favour of it.

The older physicians had obviously deduced their idea of fever, as the means by which the body was to free itself from

the materials of the disease, principally from the examination of the patient during and after the attack of fever; and it was the euphoria, as it usually takes place after the attack of fever is over, that had principally weighed with them. If we have now reason to believe that, if not all, at any rate most cases of fever take place through the absorption of specific, and in some cases perhaps organised, poisons, and if, with the cessation of the fever, the mischief which causes it vanishes, or at least becomes inert, have we not still very strong reason to surmise that perhaps it is the fever itself which has removed this mischief? And when we see that the living cells of the body are altered in their constitution and partly destroyed by the febrile rise of temperature, so that the albuminous substances are to an unusual extent decomposed (p. 5), is it not possible, we may ask ourselves, that the causes of the disease which have invaded the system have met with a similar fate in consequence of this rise in the temperature? If the observations of Heidenreich [1] are confirmed, according to which the spirillæ recurrentes exhibit movements for a long time in a temperature of 15° to 22° C. (59° to 72° F.), for a shorter time at 37° C. (98·6° F.), and that they become motionless much more quickly in a temperature of 40° C. (104° F.), we may be inclined to find in this a direct demonstration in vindication of such a conception. The experience, too, that in enteric fever, when it is constantly and thoroughly treated by heat abstraction, and the fever is by that means more or less suppressed, relapses more frequently occur than under the indifferent treatment, would lead us to fancy that perhaps the rise in the temperature contributes to the destruction of the materies morbi, and that therapeutics which succeed in keeping the temperature constantly lower are prejudicial in some degree to this action of the fever.

This conception of the import of fever, which I have already on a former occasion explained in detail,[2] and which has since then been assented to in many quarters,[3] if it should prove to

[1] *Centralblatt für die medic. Wissenschaften*, 1876, No. 29.

[2] *Handbuch der Pathologie und Therapie des Fiebers*, sect. iv. chap. i. p. 389 et seq. Leipzig, 1875.

[3] See Goltdammer, *Berliner klinische Wochenschrift*, 1877, No. 21; Leyden and Fränkel, *Virchow's Archiv*, vol. lxxxvi. 1879, pp. 184, 185.

be correct, might possibly serve as a support to a weighty objection against the antipyretic treatment. The legitimacy of this objection it might not be possible to dispute *a priori*, and we could reply to it only by an appeal to direct experience and by contrasting the favourable results of the antipyretic treatment with the less favourable ones of the indifferent treatment. But this objection, even from a theoretical point of view, would be perfectly valid only in reference to that form of the antipyretic treatment which aims at suppression of the fever; while our application of antipyresis, in which we only seek to strengthen and prolong the remissions, and not to interfere with the course of the exacerbations, would remain as good as unaffected by it.

While we limit in this way the scope of antipyresis, and postpone the artificially induced remissions to the period when they spontaneously occur, we remain even in another still more general sense in essential harmony with the traditions which have existed in practical medicine from the earliest times. The distinguished practitioners of all times have agreed in holding that it is the business of the physician to have regard before everything in his treatment to the natural course of the disease, and to regulate his procedure accordingly; and in this they were in advance of those who used to boast that they had the course of the disease entirely in their power, and did not need to trouble themselves about the natural course of things (Asclepiades, Van Helmont). We think that we take a surer course when, in a fever which threatens to prove dangerous by its continuity, we rest content with changing it into a form less dangerous for the patient, while in other respects the action of the fever is not materially interfered with.

Choice of Remedy.

I regard the employment of direct heat abstractions as the essential basis of the antipyretic treatment. My own experience, and that of others, has always more and more convinced me that the most favourable results are attained when we employ the cold water treatment in the first instance, and regard the antipyretic medicines in some measure merely as the reserve

which is to be brought into application only when the cold water treatment alone is not sufficient, or cannot for some reason or other be carried out satisfactorily. I should like to give the more prominence to this, as of late years the discovery of reliable active antipyretic medicines appears to have misled some physicians to put the somewhat inconvenient cold water treatment in the background, and to rely upon antipyretic medicines solely. Highly as I rate the importance of the latter, I believe that they attain their complete value only when they are used in combination with, and as a support to, the cold water treatment. The more I have of late years carried out the principle of trying to make the remissions stronger and longer continued, rather than of combating the exacerbations of the fever, the more frequently have I, even in serious cases, achieved satisfactory results by means of the simple cold water treatment. But even in such cases it is not altogether a matter of indifference whether we keep the antipyretic medicines in reserve or not. Only when we know that we have further means at our disposal in case of need, can we work in perfect calmness and circumspection with those which should be first employed, and in no case are we beforehand to exclude the possibility of the absolute necessity of the employment of antipyretic medicines.

Even as regards this, it has not proved to be such a simple matter for physicians to find out the happy mean. While some think that the cold water treatment is rendered superfluous by antipyretic medicines, others are possessed of the idea that all medicines are unnecessary when cold water is employed; while special hydropathists are in the habit of pronouncing even every other treatment injurious, and of maintaining that the withholding of all medicine is the condition of obtaining a favourable result. Such a condition suffers not only from its theoretic one-sidedness, but it proves also that those entertaining it have, in regard to the action of heat abstractions, not yet got beyond the usual exaggerated expectations of mere beginners. In less serious cases, in fever which is not very obstinate, we easily indeed succeed in lowering the temperature of the body sufficiently by means of strong heat abstractions, and in keeping it low as long as is necessary.

But whoever has once treated a succession of thoroughly severe cases with heat abstractions is aware of the obstacles and the difficulties which so often stand in the way of their satisfactory action, and will be glad to avail himself of every other remedy by means of which the satisfactory performance of the task is even in some degree facilitated. There are cases of fever of such obstinacy that, in spite of the constant repetition of energetic heat abstractions, it is not sufficiently subdued, and the patients in the end either die in consequence of the rise in the temperature, or run the risk of succumbing, if not to the fever, then perhaps to the severe measures employed in combating it. In those cases in which the fever seems seriously to imperil the life of the patient, it appears necessary to employ every remedy from which a diminution of the danger is to be expected, and, if it should be necessary, even several of them at the same time. The modes of treatment by abstraction of heat, and the use of quinine and other antipyretic medicines, do not mutually exclude each other; these remedies, when fittingly employed, may rather support one another. I believe that for the successful treatment of specially severe cases neither the one nor the other can be dispensed with.

Finally, the cases are by no means infrequent in which special circumstances contra-indicate the employment of the stronger heat abstractions, or at any rate render impossible such energetic treatment as might be necessary for success. In such cases we must have recourse to antipyretic medicines.

Cold baths hold the principal place among heat abstractors. In order to obtain the requisite strong remissions by means of them, it is, before all, necessary to employ them principally during the night, and to regulate them so as to correspond with the spontaneous course of the temperature, i.e. by using them more frequently as the night advances and the temperature of the patient gets lower. It is advisable to write out directions for the nurse as to the use of baths, in order that she may consult and go by them in case of doubt. Such directions for a bath during the night as I am in the habit of writing out may, in a case of enteric fever, for example, run as follows (the numbers giving the temperature refer to the temperature in the rectum):—

A bath is to be employed if the temperature is—

from	7 to 11 p.m.,	at	40° C. (104° F.),	or above it
„	12 „ 3 a.m.,	„	39·5° C. (103° F.)	„
„	4 „ 7 „	„	39° C. (102° F.)	„

It is evident that the directions will sometimes contain somewhat different numbers, according to the circumstances of the individual case; and it must be reckoned as an advantage of this way of using the bath, that we are by that means in a position to moderate the intensity of its action according to the peculiarity of the case and its state at the time. But we should always fix the limit of temperature of the bath lower for the later period of the night than for the commencement. It may also be advisable in particular cases to extend the time during which baths should, if necessary, be given—to commence, for example, at 6 in the evening, and not to stop till 8 or 9 in the morning. They ought not usually to be given in the daytime, unless the temperature should exceed a certain limit, which may be fixed, according to circumstances, at about 40·5° C. (105° F.) or 41° C. (106° F.) Cold spongings, cold compresses, and other milder forms of heat abstraction may also be employed during the day, especially if they are not disagreeable to the patient.

How often determinations of temperature should be made at night during the period for baths, will depend on the state of the individual case. As regards this, all we should exact is that care be taken never to neglect to measure it when the temperature reaches the specified limit. In slight cases it may be enough to do this every two hours, or even less often; in all cases of any severity I am in the habit of ordering it to be done every hour, and, if necessary, I have a bath given just as often. It has frequently happened to me, in specially severe cases, that in the commencement of the treatment as many as ten, or even twelve, baths were necessary between 7 in the evening and 7 in the morning, because in the determinations of temperature made every hour the limit had almost every time been again reached or exceeded. If baths were in such cases carried out quite consistently according to the prescribed rule, after a few nights the obstinacy of the fever would

often be so far assuaged that a smaller number of them would be enough, and I have sometimes succeeded, even in such severe cases, in performing the whole treatment by baths alone, without antipyretic medicines. Otherwise, when the obstinacy of the fever is so great, the temperature of the bath should be somewhat lower still, viz. about 12° C. (53·6° F.)

No doubt, the carrying out of antipyresis in this way is very unpleasant to the nurse, and the task laid upon her at night is most onerous; but the welfare of the patient must first be taken into account. And as regards the patient, it is less disagreeable for him if he has baths more frequently during the night and can then rest during the day, than if the baths are distributed over the whole 24 hours. And I may state that I have never, either in hospital or private practice, met with, on the part of the nurse, even so much as the appearance of discontent because of the exertion required on account of the night service. Finally, experience shows that by applying the system in this way, the number of the baths necessary on the whole for a patient is usually considerably less than under the older mode of treatment, according to which baths were given at a definite limit of temperature, equally by day and night; since the newer method, by concentrating the baths on the night time, has a more speedy effect.

In many even severe cases this mode of treatment is quite sufficient, and we have no need to call in the help of antipyretic medicines; while in other cases again it is necessary to make use of the reserve. The employment of antipyretic medicines is principally necessary in all cases in which there is present one of the contra-indications mentioned above to the use of baths (p. 63 et seq.), and where the fever goes on with alarming violence, and that too continuously. Even with patients suffering from intestinal hæmorrhages, we may employ quinine in antipyretic doses, but we administer it in that case in solution, with the addition of a little tincture of opium; and even in far advanced cardiac debility, in the presence of which the use of baths is contra-indicated, we may sometimes attain a successful result by means of quinine. In this way we may secure an improvement under certain circumstances, even in cases which come only late under treatment,

and with the patient so exhausted that the use of baths must not for a moment be thought of. The employment of antipyretic medicines is enjoined, moreover, in all cases in which the fever is so obstinate that we are not able to bring about satisfactory remissions by means of baths alone, even when they are thoroughly employed ; just as also in the cases in which the patient is too much exhausted by the frequent repetition of the baths, and especially when he feels chilly and shivers for a very long time after each bath. It may happen that, at the time when the temperature of the rectum again shows the height which would indicate another bath, the peripheral parts of the body continue still cold, and that therefore only a slight reduction of the temperature of the internal organs is to be expected from another bath. In all such cases, a dose of quinine given opportunely and in combination with few baths may often cause a complete remission, which brings about a real improvement in the state of the patient for some days to come, with the result that afterwards the baths alone are sufficient. And finally, sometimes even in cases not so bad, this plan may be useful for patients who suffer when the bath is frequently repeated, if by means of an antipyretic medicine in a sufficiently large dose they are enabled to pass a comparatively quiet night.

It is of great importance that, along with the use of antipyretic medicines, we should also continue the baths, provided there is no decided contra-indication to their use. Thus, for example, as regards the patient who has in the afternoon taken an antipyretic dose of quinine, the usual directions for bathing during the night apply ; and, under some circumstances, these may even be so far increased in severity that the limits of the temperature may be set at half a degree lower. The action of the quinine is then such that after the baths the reduction of the temperature is greater and lasts longer, so that far fewer baths are necessary, and they may be entirely dispensed with during the later hours of the night. It is precisely this combination of baths with antipyretic medicines which produces the strongest remissions, and the most benefit to the patient. And, in order that the reciprocal strengthening of the action of the two may be as successful as possible,

it is necessary to administer the medicines which are selected at the most opportune hours, as previously specified.

When a sufficient remission has been produced with the assistance of an antipyretic medicine, we must afterwards try and do as long as possible with the baths alone. Anyhow, the antipyretic dose should not as a rule be repeated before the lapse of at least 48 hours; I regard this rule as a fixed one, both as regards quinine and salicylic acid, and only very unusual circumstances and special necessity would induce me to depart from it. We might, indeed, by employing quinine and salicylic acid alternately, be able by means of medicines to effect a remission every night, but it is much better for the patient when longer intervals are allowed to elapse between the effects produced by the medicines. On the other hand, it may in many cases be advisable to support the action of the baths every second or third day by giving an antipyretic medicine. Many patients who are not able to bear the regular bath treatment alone can bear it quite well if the requisite baths are reduced to a smaller number, by giving an antipyretic dose of quinine in the afternoon, or a dose of salicylic acid in the evening.

Treatment of Continued Fever.

The application of the principles we have laid down to the treatment of the various acute diseases, and to the individual cases, is obvious in the main from what we have already said. The drawing up of special indications for the individual case—especially the decision of the question, whether an antipyretic treatment is on the whole required, as also of the question, what antipyretic methods are to be used and to what extent—a judicious physician will determine for himself by a careful consideration of the peculiarities of the course of the disease in the case in question, and, especially, of the idiosyncrasies of the patient. A scheme of the treatment which would be serviceable in each case cannot be drawn up.

With a view to a brief recapitulation of what we have till now been discussing, I shall give here an account of the antipyretic treatment of enteric fever, such as is at present carried

out in the clinic in Tübingen. We will assume for our illustration that we have to do with a strong man, in good health hitherto, between 15 and 40 years of age, who has been seized with enteric fever and been brought under treatment within the first week of the disease. In this case we will consider the treatment only in so far as it refers to the fever, merely premising that patients who come under treatment before the ninth day receive, as a rule, some large doses of calomel, and that with all patients the dietetic treatment is carried out in the way explained in the previous chapters.

From the time of the admission of the patient the temperature in the rectum is estimated every two or three hours, and if necessary, even every hour. If there is no danger in delay we allow the first 24 hours to pass without doing anything, in order to watch the spontaneous course of the temperature. If this is such that there is no danger to be apprehended from the continuousness of the fever, we must apply the expectant treatment for a while longer, and so on in each case, until the disease has run its course. But should the height and especially the persistence of the rise of temperature lead us to apprehend danger, not immediate perhaps, yet in the future, the rule for the baths is fixed for the next night, pretty much in the way mentioned on p. 135. With patients in any measure sensitive, the first baths are usually taken not quite so cold, at about 72° F., or else the gradually cooled baths are first used. In the later period of the night, and in the nights that follow, the bath is used from the first at the temperature which the water assumes by standing in the room; or, should the action of these baths not appear quite sufficient, it is still further cooled to about 55° F. During the night the temperature is taken every hour if the fever is in any degree obstinate, and the bath repeated accordingly. From 7 or 8 in the morning we, as a rule, let the temperature take its course, and employ at most cold spongings, cold compresses, or the like. Only when the temperature rises unusually high, to 105° F., or in other cases to 106° F., should there be also baths given in the daytime. In the event of the baths employed during the night producing a sufficient remission, the temperature usually remains in the daytime also somewhat lower than we should

otherwise expect. On the following evening the same prescription, somewhat modified if necessary, is employed as a basis for the application of the baths.

Though in former years I was fain to avail myself, for the purpose of antipyresis, of the tendency appearing in many people to a slight fall in the temperature at midday, having had recourse to baths between 11 and 2 o'clock, I have since become convinced that this tendency to fall is, at least in fevers, not always present, and that it is more advisable to concentrate the baths entirely on the night time, and to dispense with all the stronger measures in the daytime, unless an undue rise in the temperature should happen to appear.

If sufficient remissions are secured by means of the baths alone, all further antipyretic remedies are dispensed with, and baths are used every night in much the same way to the end of the disease. In this case it is in general observed that the more thoroughly and consistently the bath treatment is carried out on the first few nights the fewer baths are, as a rule, necessary on the succeeding ones. Only when sufficient and more prolonged remissions appear spontaneously towards morning are the baths entirely dispensed with; and then a rise in the temperature in the evening above 104° F., if of short continuance, may be disregarded. What degree of temperature is to be considered a sufficient spontaneous or artificial remission, depends on the idiosyncrasy of the patient. In persons, otherwise strong, in whom the action of the heart exhibits no symptoms of feebleness, it may be enough if the temperature in the rectum remains under 102° F. from 4 to 6 hours. Under other circumstances a greater decrease must be sought for, and if necessary artificially brought about.

If, as not unfrequently happens in specially severe cases, the baths during several successive nights do not produce sufficient remissions, or if, from any of the reasons mentioned previously, the patient cannot bear the baths as often as is necessary, antipyretic medicines are employed along with them. Where there are no symptoms of feebleness of the heart's action I have often been in the habit of late of giving salicylic acid in a dose of 75 grains in a neutralised solution. This dose is administered between 8 and 10 in the evening in the course

of from one to two hours, the treatment by means of the bath having been begun at 7, according to the usual directions. In other cases, I use quinine in a dose of from 30 to 40 grains, which is given in the afternoon between 4 and 7 in the course of an hour, the baths been begun as usual at 7. The consequence of this combined use of medicines and baths is usually this, that the temperature falls towards morning to 38° C. (100·4° F.) or lower, and continues for a longer period at this point. Should the action not prove so strong a larger dose must be taken next time. In every case, however, it is not repeated, as a rule, before the lapse of 48 hours; on the contrary the repetition is, when possible, put off still further, under the consistent continuance of the baths. In many cases we may conveniently succeed later on with baths alone, after a decidedly great remission has been once brought about by the co-operation of a medicine. It may be necessary in other cases to repeat the administration of an antipyretic medicine every second or third day.

I have never hitherto allowed the dose of quinine to be more than 45 grains; of salicylic acid I give in case of need 120 grains at most, divided over about three hours. We sometimes, though seldom, meet with cases of enteric fever in which the fever is so obstinate that even such doses, in combination with baths, are not enough to produce a sufficient remission. In that case, it is especially to be remarked that sometimes, when quinine does not succeed, salicylic acid proves to be more effective, and *vice versa*. If, however, both medicines fail the prognosis is very unfavourable; the sole possibility of recovery lies in bringing about a strong remission early enough, but even such cases I by no means give up for lost. Sometimes what we cannot do with a single medicine we may effect by a fitting combination of several antipyretic remedies. In former years, in cases in which quinine alone was not sufficient, I sometimes employed with success a combination of digitalis and quinine. In the morning, after the last dose of quinine, I had recourse to the digitalis, and, while continuing the baths and constantly keeping a watch over the pulse and the temperature, I administered, in the course of the next 30 hours, from 10 to 20 grains of digitalis in the form of powder. Immediately thereafter, 48 hours,

therefore, after the last dose of quinine, 45 grains more of that drug were given. Then, under the joint action of the baths, the temperature usually went down to 100° F., or still lower, until the following morning; and by that means the immediate danger was removed. Quinine and salicylic acid may also be similarly administered in combination; the former is given in the afternoon, the latter in the late evening, so that the maximum of the effect of both medicines may be obtained, while the baths are at the same time continued as often as the prescription requires. After a strong remission enforced in this way the obstinacy of the fever then shows itself so far broken that the further treatment may be conducted in the usual way.

In slight or only moderately severe cases of enteric fever, it is obvious that the employment of all the remedial methods prescribed is not necessary; we may in these cases, under certain circumstances, dispense with all; under others, with at least one or the other remedy; and we may make the selection of the remedy also in some degree dependent on external conditions, or even on the wishes or inclinations of the patient. Thus, for example, in slight cases in which the production of a greater remission appears to be indicated but once, or only a few times, I regard it of no consequence whether we respond to this indication by means of a few baths, or even without baths, by the use of an antipyretic medicine. In cases that are not too severe, a suitable dietary is really the main thing, and we may reserve antipyresis for any urgency. On the other hand, the antipyretic method of cure has its own great and decided importance, and often a truly life-saving effect, in cases in which actual danger is imminent. Where we have to do with a serious and dangerous case, I should consider it wrong if we did not give the preference to the energetic use of baths. And we should not forget that we may have to do with a case of enteric fever which, though it may appear at first slight, may afterwards develop into a severe and dangerous one.

The treatment becomes in a high degree prejudicial, if, in serious cases, intestinal hæmorrhages have taken place at an early stage, or if there is any other definite contra-indication to the use of baths. In that case it is out of our power to

avail ourselves of the most important of our therapeutic agents, and this circumstance may, in cases in which severe and continued fever supervenes, be fatal to the patient. Yet we may succeed in many cases in bringing about a favourable termination by merely treating them with antipyretic medicines. We have already stated that antipyretic remedies may be employed in intestinal hæmorrhages, and especially a solution of quinine with tincture of opium added to it; but in this case also we ought to avoid as far as possible a too frequent repetition of the medicine, and not repeat it on slight grounds before the lapse of 48 hours.

If, through the complications of enteric fever, the fever is maintained or anew increased, it is treated substantially on the same principles as the original fever. Of the antipyretic treatment in certain important sequelæ, we shall have to speak further on.

In order to give a rough idea of how often, agreeably to the principles laid down, the various antipyretic methods may come into play, I avail myself of the cases of enteric fever which I have myself treated in the clinic at Tübingen since the autumn of 1871. I here leave out of account the cases which came into my hands in so late a stage of the disease that the antipyretic treatment was either no longer practicable or no longer necessary. If we deduct these cases, there remain 99 which were under treatment at the height of the febrile stage. Of these there were treated—

Entirely without the stronger antipyretic methods	24
With baths alone	32
With baths and quinine	13
With baths and salicylic acid	9
With baths, quinine, and salicylic acid . .	7
With baths, quinine, and digitalis . . .	2
With quinine alone, without baths . . .	3
With salicylic acid alone, without baths . .	5
With several antipyretic medicines, without baths	4
	99

Among the 63 patients treated with baths—

22	received	1—10
13	"	11—20
4	"	21—30
8	"	31—40
5	"	41—50
4	"	51—60
4	"	60—80
0	"	80—100
3	" . .	more than 100

In the case of the three patients who had received more than 100 baths, the numbers respectively amounted to 111, 129, 137. To the first two of these no antipyretic medicines were administered. All three recovered completely.

The antipyretic treatment as sketched out for enteric fever is the same for every continued fever. We must, however, never forget that in a particularly malignant fever, as, for example, in severe cases of pneumonia or scarlatina, it is of still more importance to effect a strong remission as early as possible. We should therefore begin on the first night after the admission of the patient with the energetic and concentrated bath treatment, and should the baths alone appear insufficient, we should call in early the simultaneous action of an antipyretic medicine. Even in that case, it may appear that there is need of only one strong remission in order to overcome the great obstinacy of the fever during the further progress of the disease, and to bring about, as a rule, a more favourable course. Even in other diseases accompanied with continued fever, if we do not succeed in bringing about a sufficient remission in the early hours of the morning, we may, as a rule, let the exacerbation have free course during the day, provided we only take care that any excessive rise in the temperature which may occur is immediately noted and suppressed.

Treatment of Chronic Fever.

In chronic fevers the treatment must the more resemble that of acute fever, the more the fever approaches to the nature

of a continued one. There are, for example, cases of phthisis with high fever so constant that the production, from time to time, of artificial remissions, or intermissions, is clearly indicated. We usually succeed in this by the employment of quinine or salicylic acid in antipyretic doses. The production of one or more such remissions may, under certain circumstances, be decisive of the further course of the disease. The fever, indeed, in such cases, is only the result of the local disease; but it has also, in its turn, an influence on that disease, since, in consequence of the rise in the temperature, the tendency of the tissues to undergo degeneration and to break up is increased, and by that means the local disease assumes an unfavourable character. If we succeed in lessening the fever from time to time by antipyretic treatment, and in breaking through, as it were, this *circulus vitiosus*, it not unfrequently happens that the local affection begins from this time to exhibit a less unfavourable development. In cases in which extensive caseation or destruction of the lungs already exists, such a treatment has often no real influence over the further course of the disease. But there are cases with the destruction less advanced, in which some of the infiltrated pulmonary vesicles are found to be still in the condition of simple chronic pneumonia, and in which a resolution of the infiltration is still possible; and in such cases such an antipyretic treatment may, under certain circumstances, be of decided importance, while the possibility of the resolution is still maintained or increased.

The more the fever has of itself the remittent or intermittent character the less is to be expected from antipyretic doses of quinine or salicylic acid. We may, by means of these, indeed, reduce the height of the exacerbations, but we do not readily succeed in removing them permanently, and the principal action peculiar to antipyretic doses, viz. that of bringing about temporary intermissions of the fever, is not necessary in spontaneously intermittent cases; on the other hand, an energetic but regularly sustained antipyretic treatment is sometimes accompanied with pretty fair success.

In hectic fever, for example, in pulmonary phthisis, chronic suppurations, &c., the necessary preliminary for an effective treatment of the fever is attention to a proper dietary. By

means of complete rest and equable temperature, such as is obtained by constant lying in bed, the fever frequently abates after the lapse of some time, and a mode of nourishment in which proteids give place to fats and carbo-hydrates also contributes to this result. In this respect cod-liver oil, for example, may be reckoned among antipyretic remedies, as being quite as good as alcohol. Finally, in cases in which the febrile exacerbations are very considerable, or in which, by the rather prolonged application of dietetic treatment, no sufficient abatement of the fever has been attained, it is advisable to use digitalis or quinine in small but long-continued doses (p. 90), without, however, at the same time neglecting the dietetic treatment.

Antipyretic Treatment of Grave Sequelæ.

Of the numerous consequences of fever which under certain circumstances may oblige us to adopt special modifications of the antipyretic treatment, we intend to speak only of those which occur with special frequency, and which not rarely lead some to call in question the success of this treatment. We have already repeatedly remarked that the business of the physician is principally to guard against the dangerous developments of these states. But, in point of fact, these not unfrequently occur in severe fevers, either because, in spite of careful treatment, the effort to prevent them has not been successful in the particular case, or, and this especially frequently, because the cases come under treatment only after these conditions have been already more or less fully developed.

Among these sequelæ, *feebleness or paralysis of the heart* is the most frequent and serious. Where symptoms of a considerable degree of cardiac debility exist, the hope of a favourable termination, especially if we have reason to expect a long duration of the fever, is very much lessened, although not entirely abolished. A prudent and, at the same time, energetic treatment may be expected to succeed, especially in the cases in which the feebleness of the heart has come about solely in consequence of a proper antipyretic treatment having till then been neglected. The first and most urgent indication is to keep down the temperature so long as it has a tendency to rise.

The usual cold baths are generally in such circumstances no longer applicable. The employment of salicylic acid is at least in a high degree doubtful; and digitalis, which a persistently high pulse rate is often held especially to indicate, is in such cases, as long as the fever continues, not advantageous but rather injurious. The only remedy which can yet bring about recovery is quinine. It has been already stated that by means of it a sufficient remission may often be obtained; and the excessive rise in the pulse rate is often then diminished, and the heart may sometimes so far recover as to be able to bear in some degree temporary increases of temperature. In many cases the long-continued application of ice bladders to the region of the heart proves to be of service. The second indication is to quicken the activity of the heart by more direct means. Among stimulant remedies alcohol holds the first place. As soon as a rather high degree of feebleness of the heart shows itself, alcoholics should be employed in all cases; and, as regards those who have been supported by them already, the dose should be considerably increased, or we must pass from weaker stimulants to stronger. This increase must be made indeed with a certain reserve, in order that, should feebleness of the heart continue longer, we may be able to go still further, and this caution is especially necessary in cases in which a still longer duration of the fever is to be expected; but in many other diseases, in pneumonia, for example, for which the employment of alcoholics in large doses has been again recommended especially by Jürgensen,[1] we may venture to be somewhat bolder in the expectation of the speedy appearance of a definite crisis. Amongst stimulants producing a powerful immediate effect, we may name mulled wine, strong toddy, hot punch, and strong coffee or tea, and these remedies are very useful, especially in sudden collapse. Of other stimulants, I employ principally camphor and musk; and the former appears to be indicated when we consider a stimulating action to be necessary for a lengthened time, but musk appears to be better, when we have to deal with a passing danger, dependent on the feebleness of the heart.

Cerebral paralysis can be with far more certainty averted by

[1] *Sammlung klinischer Vorträge*, No. 45; Ziemssen's *Handbuch*, vol. v. 1874, p. 176.

antipyretic treatment than can paralysis of the heart, and so far as it does not depend upon gross anatomical lesions of the brain it hardly ever occurs as the immediate cause of death in cases which have from the first been treated by a suitable antipyretic method. The local application of ice bladders to the head may contribute materially to keep the functions of the brain in their normal state. I used formerly to prefer to employ cold affusions on the head in cases of severe coma and threatened paralysis of the brain, and not unfrequently, indeed, with surprising success. Even, in specially severe brain symptoms, a vesicating blister was sometimes applied to the nape of the neck; but of late, since the adoption of consistent antipyresis, such an indication has been present only occasionally in cases that have come very late under treatment, such cases as might then, however, be sufficiently treated by the usual antipyretic methods along with the simultaneous employment of ice bladders.

Results.

It has been already stated (p. 17) that wherever the antipyretic treatment has been properly applied the results have been extremely favourable. Under this treatment the fever, in itself, has lost most of its dangers; and therewith the general danger has been greatly lessened in numerous acute diseases. Whoever treats a pretty large number of cases antipyretically will soon feel convinced of this: as also he who studies without prejudice the many communications that have appeared within the last few years on the result of antipyretic treatment.

Such an extensive body of facts bearing upon various diseases has been collected that the simple statistics of mortality are enough to demonstrate the superiority of the antipyretic treatment. Many such statistics have been published,[1] especially in reference to enteric fever, and many of these comply with all the requirements necessary to make them objective and demonstrative.

If individual physicians have gone too far in their enthusiasm

[1] A comparison of the articles relating to this matter may be found in Brand's work entitled *Die Wasserbehandlung der typhösen Fieber*, p. 283 et seq., Tübingen, 1877.

over the really surprising success of the antipyretic treatment, and have imagined that, henceforth, no typhoid patient ought to die of the disease, such expectations, unfortunately, are not quite in keeping with the facts of experience. In the case of enteric fever, indeed, the danger directly due to the fever is effectively lessened by the antipyretic treatment; moreover, by its means many bad complications occur considerably less often. But all the dangers are not by that means removed. Thus, for example, perforations of the intestines take place, even under the antipyretic treatment, and they may even appear in cases which otherwise run such an easy course that an antipyretic treatment is not at all indicated. Other individual complications also dangerous to life, or particular accidents, are possible under every method of treatment; indeed, the greatest number of the cases with an unfavourable course consist of such as come under treatment too late, some already moribund, others in a condition which does not admit of antipyretic treatment or renders a sufficiently successful result from it impossible.

I give in what follows the statistics of cases of enteric fever which came under my care from 1865 to 1871 in the medical wards of the Bâle Hospital. This fever had till 1865 been treated in this hospital on the usual expectant plan, but latterly they had begun to give at times a cold or a tepid bath. Ever since 1865, baths have been regularly employed, though usually only once a day—seldom twice. Along with this, use was made of quinine and digitalis for the purpose of antipyresis, but not then according to indications as certain as in recent times. Finally, since September, 1866, after the convincing communications of Jürgensen of his results at Kiel came under my notice, the baths were employed with gradually greater frequency and gradually somewhat colder; and, along with these, antipyretic medicines were used in an appropriate way, until finally, since 1868, the method of treatment had become tolerably fixed. A determination of temperature was, as a rule, made in the axilla every two hours, by day and by night, and as often as it reached or exceeded 39° C. (102·20° F.) a cold bath was given. Besides, in cases accompanied with obstinate fever, antipyretic medicines, and especially quinine in suitable doses, were employed—in severe cases, generally every

second day. It ought to be remarked, what the statistics however make clear, viz. that enteric fever in Bâle is distinguished not only for very great frequency but also especially great intensity, and that very severe cases occur more often there than in most other places.

I. *Expectant Symptomatic Treatment.*

Year	Number of Typhoid Cases	Deaths	Mortality, per Cent.	Febrile Abdominal Catarrh and Gastric Fever	Mortality from Typhoid with Febrile Abdominal Catarrh and Gastric Fever included, per Cent.
1843	85	24		—	—
1844	34	13		—	—
1845	15	6		—	—
1846	34	17		—	—
1847	63	16		—	—
1848	25	4	30·4	—	—
1849	45	11		—	—
1850	33	11		—	—
1851	22	6		—	—
1852	35	6		—	—
1853	53	21		—	—
1854	44	13	29·5	40	15·5
1855	61	20	32·8	47	18·5
1856	77	37	48·1	66	25·9
1857	84	20	23·8	76	12·5
1858	165	44	26·7	62	19·4
1859	212	38	17·9	31	15·6
1860	158	40	25·3	65	17·9
1861	165	43	26·1	48	20·2
1862	154	38	24·7	38	19·8
1863	68	18	26·5	23	19·8
1864	86	23	26·7	77	14·1
1843–1854	1,718	469	27·3		
1854–1864	1,274	334	26·2	573	18·1

II. *With Incomplete Antipyretic Treatment.*

Year	Number of Typhoid Cases	Deaths	Mortality, per Cent.
1865 until September 1866	982	159	16·2

III. *Since the Introduction of Complete Antipyretic Treatment.*

Year	Number of Typhoid Cases	Deaths	Mortality, per Cent.	Febrile Abdominal Catarrh and Gastric Fever	Mortality from Typhoid with Febrile Abdominal Catarrh and Gastric Fever included, per Cent.
September 1866	—	—	—	—	—
to the end of 1867	339	33	9·7	63	8·2
1868	181	11	6·1	14	5·6
1869	182	8	4·4	29	3·8
1870	141	12	8·5	20	7·5
1871	131	15	11·5	32	9·2
1872	146	13	8·9	32	7·3
1873	163	17	10·4	72	7·2
1874	200	21	10·5	53	8·3
Sept. 1866–1874	1,483	130	8·8	315	7·2

To a mortality of 27 per cent. under the indifferent treatment, and of 16 per cent. under imperfect antipyretic treatment, there stands opposed a mortality of less than 9 per cent. under complete antipyretic treatment.

The numbers referring to the typhoid patients since 1865 may be directly compared with one another, because, since this time, the diagnosis of the disease has always been made from its presenting the same clinical features, and the principles of the statistics also have continued exactly the same. It turns out, accordingly, that the mortality, already considerably reduced by using imperfect antipyretic treatment, has by carrying it out more completely been reduced to about the half of what it was under this imperfect method.

The numbers before the year 1865 cannot so easily be compared, because formerly the application of the name of 'typhoid' was taken in a more restricted sense, so that individual cases, which, at a later period, would have been called slight typhoid, were placed under the head of febrile intestinal catarrh, or gastric fever. In order to make it possible to compare the numbers, two methods are at our command.

The one consists in this: That we calculate all the cases of febrile intestinal catarrh and gastric fever, both during the years when they received expectant symptomatic treatment, and also during the period when they received antipyretic treatment.

Although these for the most part are undoubtedly to be regarded etiologically as slight cases of typhoid fever, yet, when a comparison of the results under different treatment is to be made, we are accustomed justly to leave them out of the statistics of mortality, as they usually require no peculiar treatment, and on that account can bear no testimony either for or against any method. If we calculate them together, which is quite possible, according to the statistics lying before me, relative to the years from 1854 to 1864, and then repeat the calculation with regard to the whole period of thorough antipyretic treatment, the numbers of the patients treated will have equal value. We obtain, then, during the years 1854 to 1864, 1,847 patients who have received expectant symptomatic treatment, with 334 deaths, which amounts to a mortality of 18·1 per cent. among cases of gastric fever, typhoid fever, and febrile intestinal catarrh inclusive; while, during the period of thorough antipyretic treatment, we have 1,798 patients with 130 deaths, or a mortality of 7·2 per cent. Had patients died at the same rate with the latter treatment as with the former, 325 out of 1,798 cases would have proved fatal. We have seen that only 130 deaths took place; consequently 195 patients less died.

The second method of comparing the numbers is this: From the year 1865 onwards, we leave out of the statistics all those cases of which it could be presumed that in former years they would not have been regarded as typhoid cases. Such an omission is of course not quite free from arbitrariness, as an absolute limit does not exist. As, however, I had opportunities of frequent intercourse with the two physicians who, since 1859, acted as assistant physicians in the medical wards and drew up the accounts relating to the patients, seeing that often in the course of the day, at the bedside, I came in contact with one for a year and a half and with the other for six years, I could very well judge of the manner in which they were in the habit of limiting the earlier statistics. In order, however, to be quite certain, I have carried the exclusion as far as possible by omitting all that could be denominated slight cases, and also those in which the easier course of the disease might possibly be interpreted as the result of treatment. Accordingly in the second group, 1865 to Sept. 1866, 236 cases are left out, and

in the third, from Sept. 1866 to 1874, about 320 cases. The remaining numbers can then be directly compared with one another, and there exists at most this difference—that for the second and third groups the calculation was made somewhat more unfavourable than for the first. We obtain then :—

I. Under expectant symptomatic treatment:
1,718 patients and 469 deaths; mortality, 27·3 per cent.

II. Under imperfect antipyretic treatment:
746 patients and 159 deaths; mortality, 21·3 per cent.

III. Under thorough antipyretic treatment:
1,163 patients and 130 deaths; mortality, 11·2 per cent.

To the principles which were observed in the above statistics the following may be added:—

The numbers given for each separate year embrace all those cases of enteric fever which in the course of the year were treated in the hospital of Bâle; and the number for each year includes all those patients who left the hospital or died during that year. Only in the years 1865 to 1868, for evident reasons, the calculation was not made according to the exit but according to the entrance of the patients. The numbers given in connection with the antipyretic treatment therefore comprehend not only the patients who were actually treated antipyretically, but also those who, for some cause or other, did not receive antipyretic treatment.

In the number of those who died of enteric fever was reckoned, since 1865, every patient suffering from that disease in the hospital and who did not leave it alive. In such cases we did not enquire whether and how the patient was treated, or whether he actually died of typhoid and not rather of some other disease. Such questions might easily lead to arbitrary distinctions, and it is therefore better entirely to avoid them. I would again particularly enforce the remark that among the deaths that have occurred under antipyretic treatment, those cases are included which on their entrance were no longer susceptible either of antipyretic or of any other treatment, or from some cause or other were not treated antipyretically. Though in statistics, which have no other tendency than to settle, with as much certainty as possible, the actual proportions, this and a great deal else must, properly speaking, be self evident, still

I must again bring it emphatically forward, because elsewhere it has not been regarded in this light, but further arbitrary depreciations have been made.[1] Still further, among the victims of typhoid fever are included not only those who died more or less directly either from the fever itself, or from complications and sequelæ of it, but also those whose death had either no direct connection with the fever or no connection at all. Thus, for instance, among the cases which terminated fatally are found specified two patients who, during their stay in the hospital, had thrown themselves from the window and died in consequence; another in whom, after slight typhoid, ulcerative endocarditis made its appearance; another who during the course of the disease aborted, and died, undoubtedly of puerperal fever; another who, after the fever had run its course, was fully convalescent, and died in consequence of strumous disease which had previously existed, &c. It may indeed be disputed whether all such cases are to be included, or, if any, which of them; and in fact it has been debated:[2] but, just because the limits are doubtful, I settle the matter by reckoning among the victims of typhoid fever every patient in the hospital afflicted with that disease who did not leave it alive. If the line is drawn in this way, then all doubt in pronouncing on individual cases is removed, and any possible mistake can only place the results of the antipyretic treatment in a more unfavourable light. Full accuracy can easily be obtained by publishing a short history of each case that has terminated fatally.[3] It is true that during the period of the expectant symptomatic treatment before the year 1865 statistics were not drawn up quite in accordance with these principles, since, for, example, the cases of those patients who died of complications, or sequelæ, which had no direct connection with typhoid, were

[1] See *The Glasgow Medical Journal*, Sept. 1878.

[2] See Brand, *Die Wasserbehandlung der typhösen Fieber*, p. 112. Tübingen, 1877.

[3] A short account has been published of most of the cases of enteric fever which have terminated fatally in the hospital of Bâle since the introduction of thorough antipyretic treatment, namely, of 104 out of the 130 mentioned in the above statistics. See Liebermeister and Hagenbach, *Beobachtungen und Versuche über die Anwendung des kalten Wassers bei fieberhaften Krankheiten*, Leipzig, 1868. See also the printed annual reports of the medical wards of the hospital for the years 1869 to 1874.

sometimes not placed under the head of that disease, but under that representing the more proximate cause of death. If, notwithstanding this, the results of the antipyretic treatment have turned out so very favourably, its superiority is so much more certainly confirmed.

Our statistics, accordingly, show that since the introduction of antipyretic treatment into the hospital of Bâle the rate of mortality in enteric fever has been reduced to less than the half of what it was in former times.

In the clinic of Tübingen, too, the thorough use of antipyretic methods has proved very efficient in this disease. In the year 1860, after Professor Niemeyer, with whom I acted as assistant physician, had undertaken the charge of the clinic, an imperfect antipyretic treatment was begun there by the occasional use of somewhat strong heat abstractions or of antipyretic doses of quinine. Still great caution was exercised in carrying out these heat abstractions, which were not used more than once a day, except in rare instances. At a later date the use of them became even more rare than formerly. After I had undertaken the charge of the clinic, in the autumn of 1871, a thorough antipyretic treatment was carried out, and gradually it became the great object of this mode of treatment rather to bring about stronger and longer intermissions of the fever than to combat the exacerbation. The results were as follows:—

I. During the period of imperfect antipyretic treatment, from 1860 until the autumn of 1871, 61 enteric fever patients were received; of these 14 died; the rate of mortality therefore amounted to 23 per cent.

II. During the period of thorough antipyretic treatment, from autumn 1871 to March 1880, 110 patients suffering from the same disease were received; 6 of these died; therefore the rate of mortality amounted to 5·5 per cent.

In these statistics of the clinic of Tübingen the same principles were followed as in those of Bâle. A closer inspection of details I must delay until another opportunity. But I must mention here that patients were frequently handed over to the clinic in Tübingen for whom all active treatment came too late. Thus, then, of 6 patients who have died since the introduction of thorough antipyretic treatment, 4 had come under treatment

only after the lapse of the second week. A fifth patient died of perforation of the intestines, and the sixth of a pneumonia which appeared late in the course of the case. Several were brought to the hospital very late; and although on entering they gave evidence of very considerable weakness of the heart along with excessive frequency of the pulse, they, nevertheless, recovered. On the other hand, even among those who entered late, there were individual cases in which when they came under treatment no special danger any longer existed.

Against the application of statistics of results to therapeutic questions in the earlier decades of the century, the charge must generally be brought that those who compiled them did not make use of that strict method of calculation of the probability, by which alone it could be decided how far one might with certainty assume that the difference of result was not simply accidental. This charge, the justice of which cannot be altogether denied, so often repeated by theorists, has essentially contributed to bring discredit on therapeutic statistics, even when they were satisfactory in every other requirement. This want was especially perceptible in certain cases, in those, for instance, in which under the above-mentioned statistics of the clinic of Tübingen the numbers were too small to admit of the usual mathematical methods being employed, while yet the facts were of such a kind as to bear an aspect the very reverse of unimportant to an unprejudiced inspection. Since I have given a comparatively direct and simple method of making such calculations,[1] it is no longer difficult to apply the method of calculating according to probability to such questions; and this method must be employed in order to fix the degree of im-

[1] On calculation of probability in its application to therapeutic statistics, vide Volkmann's *Sammlung klinischer Vorträge*, No. 110, Leipzig, 1877. Since that time Hagenbach Bischoff has submitted this subject to an entirely new method of examination, and has arrived at exactly the same formulæ which I had previously found out in another way. See E. Hagenbach Bischoff, 'Die Anwendung der Wahrscheinlichkeitsrechnung auf die therapeutische Statistik und die Statistik überhaupt,' *Verhandlungen der Naturforschenden Gesellschaft in Basel*, vol. vi. 1878, p. 516. On the transformation of the respective formulæ by an elementary method, vide H. Kinkelin, 'Smaller Mathematical Communications, IV.,' in the *Bericht der Gewerbeschule zu Basel*, 1876–7, p. 11, Bâle, 1877.

portance of the differences discovered. Thus, then, in support of the assumption that in the statistics of the clinic of Tübingen the more favourable rate of mortality is not simply the result of chance, we have a probability of 0·999545. More than 2,000 to 1 can be wagered that the difference of the results is not accidental.

With regard to such large numbers as the statistics of the hospital of Bâle contain, the older methods might be employed quite as well as my formula. By these we obtain, in support of the exclusion of chance, as I have already shown, a probability which practically is no longer distinct from absolute certainty. It is true that individual authors have endeavoured to throw doubt on the formula which I have used in these statistics by the remark that the probability assumed by me for the exclusion of accident is greater than the empiric probability that night will be succeeded by day.[1] This objection to my method of calculation is set aside by the statement that the older methods yield exactly the same results, and it can only proceed from those who have not understood the strictly mathematical derivation of the formula, and, indeed, it can only be ascribed to a want of understanding of the subject. The probability, that the more favourable rate of mortality during the period of antipyretic treatment does not depend on chance but approaches very near to absolute certainty, is, in fact, greater than the empiric certainty that every man will die. And as no result of calculation according to probability can ever stand in opposition to the result obtained by intelligent reflection, so it is with the case in question. Whoever tests the numbers with this intelligent reflection will, even without calculation, be convinced that the difference of the mortality in the different groups cannot possibly be accidental, or, to speak more correctly, that the exclusion of accident in this case has almost an absolute certainty.

As, however, I have repeatedly stated,[2] our task with reference to such questions is not finished when we have settled this more formal part of the subject. On the contrary, besides

[1] J. Hirschberg, *Berliner klinische Wochenschrift*, 1877, No. 21; E. Ricklin. *Revue mensuelle de Médecine et de Chirurgie*, August, 1877, p. 638.

[2] *Deutsches Archiv für klinische Medicin*, vol. iv. 1868, p. 423; *Sammlung klinischer Vorträge*, No. 110, 1877, p. 936.

the mathematical analysis, that part of the proposition is still to be solved which I have designated the clinical analysis. And this part is usually by far the more difficult, on account of the complication of circumstances which often exists, and which may make it difficult, or even impossible, to decide how far the difference of results depends on a factor which comes immediately before the eye, or on other factors known or unknown. Thus, even the above-mentioned statistics of the hospital of Bâle, and the application of the method of calculating according to probability, afford no proof that the more favourable rate of mortality during the period of antipyretic treatment was actually and solely the result of that treatment. The calculation only proves with almost absolute certainty that the difference in the mortality was not accidental. At the same time, however, the existence of a difference is universally shown in the continually operating causes ; calculation can give no explanation as to what kind of difference this is ; to settle that question a special and thorough examination is essential. This examination has been already undertaken in every direction with all possible care, but a repetition of the details, which have already for the most part been communicated on other occasions,[1] would lead us too far. I may only remark that enteric fever in Bâle has more recently lost nothing of its former malignity ; and that neither the improvements in the hospital arrangements, except in so far as they have facilitated antiypretic treatment, nor the somewhat earlier entrance of patients, nor, finally, the various changes in their treatment, have exercised any real influence. The only constantly operating cause to which the change in the rate of the mortality can be ascribed is the introduction of the antipyretic treatment. Finally, if we consider that wherever a similar antiypretic treatment has been carried out with the necessary thoroughness, a similar change in the rate of the mortality has been obtained,[2] then, again, it is proved, with almost absolute

[1] See Liebermeister, 'Bericht über die Resultate der Behandlung des Abdominaltyphus im Spital zu Basel,' *Deutsches Archiv für klinische Medicin*, vol. iv. 1868, p. 413 ; Liebermeister and Hagenbach, *Beobachtungen und Versuche über die Anwendung des kalten Wassers bei fieberhaften Krankheiten*, Leipzig, 1868 ; *Jahresberichte über die medicinische Abtheilung des Spitals zu Basel*, 1869 et seq.

[2] See Brand's comparison, loc. cit. 1877, p. 283.

certainty, that there really exists in antipyretic treatment the one constantly operating factor.

There are many places in which, even under indifferent treatment, enteric fever has a much smaller rate of mortality than in Bâle. But still even in such places antipyretic treatment is not superfluous, for, in fact, even there, many men in the full bloom of manhood fall victims to the disease, several of whom might possibly have been saved by this treatment. As an instance, I bring forward the first full statistics that have been published, with a comparison of numbers, on the results of antipyretic treatment, viz. the statistics of Jürgensen, from the medical clinic in Kiel, which were drawn up according to the very same principles as those firmly held by us in reference to the hospital of Bâle and the clinic of Tübingen. In the clinic of Kiel between the years 1850 and 1861, out of 330 cases of enteric fever, 51 died under indifferent treatment, amounting to 15·4 per cent. From 1863 to 1866, out of 160, who were treated in a thoroughly antipyretic way, only 5 died, being at the rate of 3·1 per cent.

In other febrile diseases too, antipyretic treatment has proved successful; yet hitherto no disease has given us such extensive material for statistics as enteric fever. In general, it is to be expected that the success of the antipyretic treatment will be especially great in those diseases in which the danger proceeds chiefly from the fever and its consequences; and that the more the danger of any disease depends on localisations, the less will antipyretic treatment be able to accomplish. Thus, for instance, in true typhus fever, in which the dangers of the febrile condition come more into prominence, antipyretic treatment would give promise of greater success than in enteric fever. Accordingly, we meet with accounts of good results very recently, and without referring to the older experiences of Currie and his successors.[1] On the other hand, it must not be expected that in acute croupous pneumonia, in which the local affection is of much greater importance, the success of the antipyretic treatment will ever be so great as in enteric fever.

In the hospital at Bâle, since the middle of 1867, the anti-

[1] Fr. Mosler, *Erfahrungen über die Behandlung des Typhus exanthematicus*, Greifswald, 1868; Brand, loc. cit. 1877, p. 255 et seq.

pyretic treatment of pneumonia has been carried out in the same way as in enteric fever, and it has yielded essentially better results than the usual expectant symptomatic treatment. In Bâle malignant asthenic (typhoid, bilious) pneumonia predominates; and it must also be taken into consideration that in this disease, still more frequently than in enteric fever, the patients are only sent into the hospital at a time when it is too late for the application of remedies. In private practice, the last fault is of less weight, and antipyretic treatment can there accomplish more, because, on an average, it can be begun earlier.

In what follows, the rate of mortality among patients suffering from pneumonia in the hospital of Bâle, during the period in which I practised thorough antipyretic treatment, is compared with that of former years.[1]

I. *Under Indifferent Treatment.*

Years	Number of Pneumonic Cases Treated	Died	Mortality
1839–1848	223	55	24·7 per cent.
1849–1857	197	49	24·9 ,,
1858 to middle of 1867	272	71	26·1 ,,
1839 to middle of 1867	692	175	25·3 per cent.

II. *Since the Introduction of Antipyretic Treatment.*

Years	Number of Pneumonic Cases Treated	Died	Mortality
Middle of 1867 to middle of 1871	230	38	16·5 per cent.

These statistics of pneumonia are drawn up according to the same principles as those followed in the statistics of enteric fever. It may be stated among other facts that, since the introduction of antipyretic treatment, all the cases have been included which, during that period, entered the hospital; and among the cases of death those especially have been included which were not treated antipyretically. Were we to reckon only

[1] See C. J. Major, *Ueber die Behandlung der acuten croupösen Pneumonie mit kühlen Bädern*, Dissertation, Bâle, 1869; Fismer, 'Die Resultate der Kaltwasserbehandlung der croupösen Pneumonie im Baseler Spitale,' *Deutsches Archiv für klin. Med.*, vol. xi. 1873, p. 391.

those cases in which baths were used we should have 152 patients and 16 deaths, i.e. a mortality of 10·5 per cent.

The probability that in the above statistics the more favourable rate of mortality since the introduction of antipyretic treatment is not the result of accident, is equivalent to 0·99713, or 348 to 1. With regard to clinical analysis, I may refer to the work of Fismer.

In conclusion, I would again suggest that the antipyretic method, though it has justified its claims by its extraordinary success, is still comparatively new, and that, therefore, we must not think of regarding it as permanently established and completed. We ought rather to cherish the hope that further investigation will succeed in rendering it more efficient, and possibly also more pleasant for the patient. Perhaps the methods of applying it hitherto may yield us still better results if they are carried out with more thoroughness and circumspection. Especially, however, I place my hopes on the modification of the method minutely described above, which consists not so much in striving to suppress the exacerbations as to prolong and strengthen the remissions of the fever.

ANTIPHLOGISTIC METHODS OF TREATMENT.

BLOOD-LETTING. TRANSFUSION.

BY

PROF. THEODOR JÜRGENSEN,

OF TÜBINGEN.

TRANSLATED BY

MATTHEW HAY, M.D.,

PROFESSOR OF MEDICAL JURISPRUDENCE, UNIVERSITY OF ABERDEEN.

ANTIPHLOGISTIC METHODS OF TREATMENT.

INFLAMMATION and its treatment have for many centuries constituted, the former the germ of pathology, the latter the germ of therapeutics.

'Inflammatory' diseases—among these was included a large number of diseases which are indeed attended by inflammatory processes, but in which the inflammation is too inconsiderable to exercise much appreciable influence on the character of the whole disturbance. This, however, was no essential mark in the usual conception of the *morbus inflammatorius*; inflammation in our sense, local inflammation especially, could hardly have been found in a considerable number of these *morbi inflammatorii*. The main distinction lay in the disturbance of the body generally, and the quality of the blood. Particularly a fever definable by special symptoms—we may say, in general, a fever running its course with unenfeebled activity of the heart—was of importance in distinguishing the inflammatory diseases. Such a fever, however, is usually present at the beginning of most acute diseases, at any rate when strong individuals are attacked. It is not therefore surprising that, among our ancestors, the large class of *morbi inflammatorii* consisted of many different diseases.

This method of distinguishing inflammatory diseases furnished at once a basis for their treatment. Antiphlogosis was associated with *morbus inflammatorius* infinitely more closely and firmly than antipyresis to-day is with an increased bodily temperature. To discontinue antiphlogistic treatment appeared to most physicians more a crime than a mistake. To the majority of practitioners, the diagnosis *morbus inflammatorius* was, without anything further, an indication for the carrying out of antiphlogosis, which was done chiefly by means of vene-

section. And even the physician who held a prominent place among his contemporaries seldom asked himself the question whether blood was to be withdrawn; the question more frequently was—When and to what extent this is to be done?

I might quote a few examples, in order to show the difference between present and former times. The chapter on *Variolæ* in the Commentaries of Van Swieten, belonging to a comparatively modern period, is well fitted for this purpose.

The infectious, as well as contagious, nature of small-pox was as well known as it is at the present day, and yet, with certain restrictions, it was included among *morbi inflammatorii.*

Sydenham has already defined *variola* to be inflammation (different in kind, however, from other inflammations), sometimes of the blood and sometimes of the other humours.

Van Swieten thus concludes a somewhat long discussion in which he establishes the class of the disease:—'All these things seem sufficiently to prove that *variola* may be classed with inflammatory diseases, though it has many peculiarities by which it is distinguished from other inflammatory diseases.'

With respect to the fever preceding the appearance of the pustules, it is said, in the words of Boerhaave, 'This disease therefore, akin to every acute inflammatory disease, can in this state be with difficulty distinguished from it.'

And, further, says Boerhaave, 'Here the universal method [1] may evidently be applied, and such measures ought to be taken as are found of value in every inflammatory disease, lest the inflammation should degenerate into pus or gangrene. Since this method succeeds in all other cases, there is nothing here to prevent the variolous disease from being without an eruption.'

From the Commentaries on this paragraph (1393) I extract a few words. 'So long as a certain antidote to variolous contagion is not yet known, art can oppose to this disease no better remedies than those which are found to be of use in other diseases, producing similar symptoms. It has been truly said that this contagion, whilst in action, will produce symptoms of inflammation, and that sometimes the disease deceives even skilful physicians, by appearing so similar to other acute inflam-

[1] Blood-letting.

matory diseases that a certain and absolute diagnosis is only to be made when papules appear on the surface of the body. It then seems to be in the highest degree reasonable that the universal antiphlogistic method should be practised in the beginning of the disease, while the symptoms of inflammation are present.'

In conclusion, the introduction to the succeeding paragraph may be quoted :—'It (the universal method) consists in this: Blood is to be withdrawn.'

That men like Sydenham, Van Swieten, and Boerhaave, in their treatment of small-pox, were extremely cautious in practising venesection, is well known; but 'contemporary with these men of the highest worth and intelligence,' says Wünderlich,[1] even of this century, 'lived a large number of most thoughtless, ignorant practitioners.'

This is not the place to trace the gradual course of the revolution which the doctrine of inflammatory diseases has undergone ; it is sufficient to briefly sketch its present position.

The general term, 'inflammation,' according to the earlier acceptation, and also 'antiphlogosis,' have now come to be more precisely defined, and thus greater clearness is also procured for the treatment. *We have now, along with antiphlogosis, the antiseptic and antipyretic methods.* This is a gain for which we are essentially indebted to a deeper insight into the development of diseased processes; anatomical, physiological, and etiological research has each contributed its share to the progress that has been made.

The healing of every external wound is accompanied by a course of inflammatory processes, but such a local inflammation is not necessarily a source of danger to the whole organism. The maxim of Boerhaave, 'Fever is the inseparable companion of inflammation,' is no longer absolutely valid. If general suffering ensues, it can only be ascribed to something deleterious penetrating from without, not necessarily connected with the original wound, or with the processes of repair. By keeping out this, it is possible to confine the local process to the part affected. Such is the *antiseptic* method of Lister and

[1] *Geschichte der Medicin*, p. 233.

his followers, which is assisting operative surgery to constantly new successes.

The *antipyretic* method of treatment also takes an honourable place in the therapeutics of the present day. It is more and more generally acknowledged that the majority of *morbi inflammatorii* have a very restricted course as regards time. The injury which excites tbe disease can only act for a short time, and if the body can hold out during that period, then the danger which threatens it is only an indirect one; indirect, as it proceeds from those points which are placed in an abnormal condition by the primary action of the cause of the disease—the so called sequelæ. The great business of the physician, therefore, is to uphold the power of resistance of the affected organism during the allotted time in which the cause of the disease maintains its strength. In order to accomplish this task he must know in what way a hurtful influence is chiefly exercised. Experience teaches that, at any rate, one of the two active joint factors—the poisoning and the fever—may be impeded in its hurtful action. We select from the whole of the febrile symptoms that one which has the most serious consequences, the intensification of bodily heat, and which we must, therefore, attack. At the same time the supply of nutriment, which has now only become practicable, is effected as far as possible—nutriment readily capable of change and of transformation into vital energy. Thus an enemy is kept at a distance, and the way is laid open for the assistance of a friend.

If the success of antipyresis, recorded by most physicians, is not equal to that of antisepsis, and if, perhaps, equal success is not even attainable by the former, we need not wonder. The antiseptic method is prophylactic, and, under right management, prevents the intrusion of an active cause of disease; the antipyretic method, on the contrary, has to deal with the full strength of this, when it has already become active, and has drawn the whole organism into sympathetic suffering. The latter can only meet the evil by indirect ways; the former meets the local disease directly at the affected part. It is an invaluable gain to have a clear perception that a direct procedure in inflammatory disease, in the sense of overpowering the cause of the disease by something that will annihilate it,

is impossible. An universal method of treatment for inflammation, according to the notion of our ancestors, will hardly again be sought for. And yet this is the germ of the doctrine always inculcated by the various schools of the past; they strove to find out a treatment which, directly, universally, and under all circumstances, must be effectual against inflammation.

When we in these days, with conscious modesty, choose as the point of our attack only one danger, doubtless, however, the chief one, the reproach of *one-sided symptomatic treatment* is cast on us by theorists and practitioners, who, appropriating the views of others, dispense with any experience of their own in this direction. The fact, that we the more frequently and quickly attain the main object, viz. the cure of the patient, is less observed.

By the development of antipyretic and antiseptic treatment the department of antiphlogosis is essentially circumscribed. And even the ground that remains to it is still further limited. The question, '*How, under given circumstances, is the affected part to be treated?*' occurs oftener than, '*How is inflammation generally to be treated?*'

What is to be done when the first symptoms of a probably perforating peritonitis appear? Formerly the answer would have been, 'Antiphlogosis, local as well as general;' now it is, 'Lessening of the peristalsis:' only in that way can the local disease be confined to the place of its origin. Generally, *local indications have attained more and more value as against general ones.* Special individual treatment is thus more and more incumbent on the practitioner; but he must have regard to the nature of the locality of the inflammation. Thus again a fragment is broken off from the general therapeutics of inflammation, and is added to special therapeutics.

The treatment, from a general therapeutic standpoint, of what remains, must—so soon as it aims at being something more than a simple summing up of what *has* been, and by custom *is* still—comprise in itself a criticism of the past, along with an attempt to construct comprehensible indications on the ground of the present. If we would not offer sacrifice on the altar of the opinions of the day, pretty frequently, it is true, hallowed by venerable age, then must a *non liquet* not seldom be heard.

In order to have a firm foundation, we must first consider somewhat minutely the *changes* which occur *in inflammation.* One thing appears certain; in every inflammation a change of the wall of the blood vessels exists. This, in its essential nature, is still unknown, and not demonstrable by optical and chemical means. It is a physical change, which may be described as a greater penetrability for the contents of the blood vessels; and along with it increased adhesion takes place between the walls of the blood vessels and the blood itself. From the changed vessels exudes a part of their contents, varying in composition according to external conditions, and consisting of dissolved and suspended constituents in variable proportion. Penetrating into the adjacent textures through tissue fluid, with which it mixes both directly and by diffusion, changed in many ways, the inflammatory stream spreads itself out, following the mechanical conditions present. It depends on the resistance offered to it, how great the extent of the ground occupied, how high the pressure at each individual point, the tension, the mechanical injury may become. This mechanical action of the changes in inflammation is not less important for the therapeutics than the chemical action. Along with these two actions comes into consideration the capability of the inflammatory stream to spread the disease by flooding the tissues, and carrying with it corpuscular elements, putrefactive germs, &c.

That the peculiar constituents of the tissues are also affected in inflammation admits of no doubt.

The directly acting primary cause of the inflammation, of whatever nature this may be, very rarely confines itself exclusively to the vessels; it almost always involves the whole of the tissues constituting an organ. Every mechanical, every thermal, and every chemical stimulus affects a surface, the smallest part of which is occupied by vessels. If it does not result in destruction or in death of the part of the body injured, then, indeed, further changes make their appearance under the form of a legitimate inflammation, affecting especially the vessels.

It is also improbable that the extremely abnormal conditions of nutrition of the organ, which are produced by the changes in the function of its vessels, leave the organ itself untouched.

For, of course, in order to maintain the undisturbed well-being of each part of the body, its continual contact with healthy blood, flowing through it from vessels acting at least in an approximately normal manner, is absolutely necessary.

Along with the fundamental view, which looks for the essential nature of inflammation in the physical change of the wall of the vessels, the circumstances mentioned deserve full attention from a practical standpoint.

How does inflammation abate?

The answer, starting from the main point, is this: it abates by the wall of the vessel again becoming normal; and this can only take place by means of a sufficiently full action of healthy blood within it. Everything, even the further repairs, depends on the removal of the products formed during the continuance of the specially active inflammatory changes, perhaps the removal of a dead portion of the tissues, with a compensatory filling up of the space it had occupied.

The general therapeutics of inflammation has, therefore, under all circumstances, to hold fast to this requirement, viz. *that a sufficient and satisfactory supply of healthy blood must reach the seat of the inflammation.*

This aim remains firm; even when in an individual case an apparent departure from it seems to be necessary, it is always only a necessity limited by time and situation.

When, for example, a sero-fibrinous pleurisy is accompanied in its very commencement with such a copious effusion that life is endangered by the resulting compression, the physician will not hesitate to tap the fluid, though he knows that in a short time a new collection usually follows. Here the composition of the blood is further impaired, and less favourable conditions for the final cure of the local inflammation are created; but this is done in order to preserve the whole body, and to make recovery quite possible and attainable.

The rule for every course of action which may be carried out in the treatment of inflammation is, of course, to be taken from general principles.

Let us consider individually, and with all brevity, the usual modes of procedure.

It is sufficient to refer to the old axiom, 'cessante causa

cessat effectus,' to make valid the rule that always and everywhere the *primary cause of the disease is to be removed*, or at least, as far as possible, weakened.

Not unfrequently, however, difficulties stand in the way of the accomplishment of this object; and thus, in removing the foreign body which has forced its way in from without, the question may very naturally arise, whether the operative measures necessary for that purpose are not more injurious than would be its removal, prudently and spontaneously brought about, in the ordinary course of natural cure. It is possible that the extensive exposure, which is connected with forcing one's way into a hitherto uninjured tissue, may produce greater dangers than are caused by the simple presence of the inflammatory process in the living body, without anything further. Military surgery affords sufficient proofs that many a time it is more advisable to leave a foreign substance in the body than to remove it by a deep-seated operation. In internal medicine, also, a similar consideration is often of great practical importance. No one doubts that peritonitis may proceed from constipation. But if there exist already distinct symptoms of such a peritonitis arising from a stoppage of the fæces, then the better way will frequently be to quiet the intestines by opium, rather than to purge them and so to attack immediately the original cause of the inflammation.

Thus, then, even this simple maxim must not be recklessly carried out.

Further, *everything is to be avoided which might, on its side, cause an increase of the inflammation*. We must distinguish between the approach of a new cause of inflammation and the action of irritants, which strengthen an existing inflammation, but, under normal conditions, are of themselves incapable of initiating such.

If, for instance, in an injury, the cuticle or cutis has been destroyed, then the part laid bare is exposed to the influences of the outer world in quite a different way from what it was when uninjured. Fluctuations of heat, evaporation, foreign bodies floating in the air, combine to produce an effect which was entirely, or at least in a great measure, impossible so long as the protecting covering was uninjured. The difference in

the behaviour of subcutaneous injuries and of those which are accompanied with destruction of the skin is sufficiently well known. The first office of therapeutics under these circumstances is to procure a reparation of the lost protection; and this problem has been most fully solved by the method of Lister and his followers. The details of the antiseptic treatment are not appropriate here.

The second point is of great importance practically; we are not always very clearly conscious of it, or at least we do not always act as we would necessarily do if we kept its importance constantly before our eyes.

In the simplest circumstances, such, for instance, as a traumatic solution of continuity offers, no one doubts that the injured limb requires *rest*. For we see how, after every transgression of this rule, the healing process is disturbed, and the inflammation is excited anew. This is also the case with inflammation in joints or bones, whenever its course in these is somewhat slow. It is well known that many a traumatic inflammation in the knee joint, which was at first slight, under improper treatment suppurates, and this ends in the loss of the limb, or even of life itself. Instead of at once giving it complete rest, people trust to alterative or resolvent plasters, salves, and such things. People often proceed in exactly the same manner with inflammation of the vertebræ. It is only with difficulty that the laity can be brought to understand that complete rest is the essential condition of cure: the physician forgets this, and yields to the desire that an 'attempt' may at least be made to use the inflamed limb, even if it were only within limits.

Internal medicine also can bear testimony to offences against this cardinal axiom. A pleuritic patient, who, while there is a small amount of exudation, still moves about, in doing so, as a matter of course, makes freer and more frequent respiratory movements, and will, as a general rule, experience in a short time a considerable increase of the effusion, and perhaps its change into one of a purulent character. Rest in bed, on the other hand, even where there is considerable exudation, appears to be in itself sufficient to remove the exudation in a short time. I have for a long time contented myself with this

extremely simple course when no operative procedure was necessary. From the same point of view we must judge the use of narcotics for the violent cough which accompanies inflammation of the mucous membrane of the respiratory passages, and the application of cold or digitalis in pericarditis. These remedies act antiphlogistically by inducing rest.

The necessity of giving as much rest as possible to the inflamed parts may easily be theoretically proved by the general circumstances accompanying inflammation.

With every movement, so long as it lasts, the state of the circulation is changed; for an inflamed part this change is directly injurious. Dragging, stretching, and pressure of the blood vessels of the part, as also changes in the resistance, cannot be avoided, and thus the conveyance of the blood, which alone can make the restoration of the wall of the vessels possible, is interrupted ; and so much the more, the more freely and frequently the movement is made.

Along with this comes often into consideration the spreading into the neighbourhood of the existing exudations, which are capable of a phlogogenic action. Thus the inflammation is spread as well as aggravated.

The movement of an inflamed part may, in this view of the case, be justly regarded as a new mechanical injury to the part.

The principal object in every treatment of inflammation is to convey locally to the injured vessels a quantity of healthy blood, sufficient for their restoration.

The ways to be taken in order to reach this end, however much they may seem to separate from each other, yet all meet together at the goal ; an opinion as to the suitableness or unsuitableness of each method will depend on a general consideration of the case.

In order to get a general survey, a classification of the different methods may be attempted according to the main standpoints ; it is, however, by no means strictly practicable.

They may be divided into—

1. Direct methods, influencing the local blood circulation.

2. Indirect methods, influencing the local blood circulation through the instrumentality of the nerves.

3. Empiric methods, whose mode of action is unknown, or not sufficiently known.

As I intend in other parts of this work to give more particular consideration to these methods, I confine myself to a few general remarks in this place.

It is well known that an inflamed limb is less painful, feels less hot, looks less red, and becomes less swollen, so soon as it is laid at rest in such a way that the returning blood has less resistance to overcome. On this account the technical expression 'elevation' (*Hochlegen*) has been introduced.

What takes place under these circumstances is physically clear. In the entering vessels, which run from the centre towards the periphery, gravity offers resistance; in the returning ones, those making their way from the periphery to the centre, the force of gravity aids the flow of blood. That in this way very important changes in the circulation may ensue has been most unequivocally proved by the measurements of warmth made by Julius Wolff.[1] The temperature of the closed palm was brought down five degrees, simply by long-continued elevation.

By elevation the quantity of blood existing at the moment in any particular part becomes smaller; it can easily be seen, nevertheless, that without something else no unfavourable conditions of nutrition are thereby caused. The important point is, not that as much blood as possible should flow through the vessels to the seat of the inflammation, but that this blood should be as healthy as possible. Venous blood and lymph are more quickly removed from the seat of the inflammation in the elevated limb. By this means there ensues an abatement of the tension of the tissues, which, by lessening the resistance offered, is of advantage to the easily compressible vessels coursing in the inflamed part, and especially to the capillaries. As the chief hindrance is in these and in the smallest veins, which, physically considered, lie near them, it is just here that the increased resistance of friction, of adhesion between the blood and the wall of the vessel, so emphatically insisted on by Cohnheim, makes itself felt; and therefore a lessening of the

[1] 'Ueber Schwankungen der Blutfülle der Extremitäten,' *Archiv für Anatomie und Physiologie*, year 1879, 'Physiolog. Abtheilung,' p. 161 et seq.

tension outside, which is doing its best to lessen the calibre of the blood vessels by pressing their walls nearer to each other, will be well calculated to increase the rapidity of the flow through the now widened tubes.

The consideration, theoretically possible, that the quantity of arterial blood may become too small by the increased resistance at the seat of the inflammation is not likely to have much weight. Should it already have come to such a vast diminution of the strength of the heart, as might then be supposed, the chief anxiety for the moment would more frequently be to preserve life than to treat the inflammation.

By greater or less elevation it is possible to regulate within wide limits the inflow and outflow. Thus this proceeding, wherever it is practicable, is of high value, as experience at the bedside has long ago taught us.

As a means of removing inflammation, *pressure* from without has in various ways been applied. As a number of collateral conditions are involved, this is somewhat more complicated. Nearest to this very simple proceeding stands the so called *massage.* The fundamental principle of this method is to effect by mechanical action a better outflow of venous blood and lymph from the inflamed part. By the various prescribed manipulations it is possible to bring about a direct evacuation of the efferent vessels, and, at the same time, an acceleration of the movement of the fluid in them ; on the other hand, however, there must ensue a mechanical stimulation of the nerves of the vessels, the final result of which can hardly be anticipated with certainty. The sphere of massage is restricted to those inflammations which run their course slowly, and in those parts that are accessible from the surface, or possess a fairly considerable vascular connection with it. In acute inflammations any advantage from massage could indeed hardly be expected ; and just as little should the attempt be made to dissipate chronic inflammatory changes in the brain and spinal chord by kneading, though it be ever so energetically and correctly carried out.

Bandaging the inflamed part has to deal with still less simple effects. First of all, it prevents movement to a certain extent, and thus induces rest. Then the properly

applied bandage, ascending from the periphery towards the centre, acts mechanically, like massage, by pressing the fluids into the efferent lymph vessels and constricting the lumen of the vessels. Furthermore, it must be taken into account that, as, in regulating the course of a stream, the channel, if too broad, is by degrees narrowed in order to induce a quicker flow in the remaining part, so here, the more superficially situated vessels are compressed, and a larger amount of fluid is thus conveyed to those more deeply situated. It may be readily supposed that, as in the river a quicker flow prevents the deposit of suspended particles, so under these changed conditions the arrest of lymph corpuscles, blood discs, &c., is hindered. It is certainly, however, of great importance that, through the diminution of the calibre of the vessel, an increase in the rate of the current and a quicker discharge of the whole contents of the vessel is brought about.

It might also be suggested that by the application of each bandage the amount of heat given off externally is diminished, and this ought to be taken into account.

The necessity of the fulfilment of the condition, that bandaging ought to promote the circulation, appears distinctly from a consideration of bandages that are injurious. It is sufficiently well known that bandages that are improperly or too tightly put on always produce, by impeding the blood-flow, an aggravation of the inflammation, which may proceed even to actual necrosis. Our aim must, therefore, be constantly fixed on the maintenance of a sufficient and sufficiently regular blood and lymph circulation. Technical blunders are most likely to be committed when one tries, by continuous pressure, to force the absorption of the inflammatory deposits of an inflammation that has run its course.

Surgical experience teaches that *incisions* more or less deep in an inflamed part are, under certain circumstances, essential for the preservation of the tissues.

At first sight it might appear strange that an operation of such a kind as is believed to excite, of itself, inflammation should diminish it.

Surgeons consider that such incisions 'relieve tension' ('*entspannende*'), and this technical expression hits the nail

on the head. One wishes, by dividing the tissues, to open a way towards the outside for the fluids which are retained under high pressure, and thus to facilitate the circulation of the blood and lymph in the vessels (now burdened with less resistance) which course through and nourish the tissues. This fundamental idea has been already mentioned; but another factor is added to it. The incisions necessarily divide a number of vessels, which in consequence become thrombosed: the number of exuding vessels is lessened. The inflammatory exudation now takes place from a smaller number of vessels. The tension of the tissues, therefore, supposing the inflammation to be equally strong, can no more, even temporarily, be so great as formerly.

By means of deeply made incisions the 'reaction' that is wanting—viz. the inflammatory symptoms which have not yet manifested themselves in their full extent—is often produced because the circulation of the blood through the inflamed part is made possible and necrosis is thus prevented.

The case is somewhat different when the incision permits a part removed from the source of its nutrition to be brought again into connection with it, as is the case, for example, in purulent periostitis. The whole of the circumstances just mentioned must therefore be taken into consideration.

Local blood-letting, practised directly on the inflamed part, or even in its neighbourhood, must be judged from various points of view. The end to be attained is not always the same; at least it does not always appear to be so. The final aim indeed remains always firm, viz. a sufficient quantity of healthy blood is to be brought to the affected part.

It may appear desirable, by lessening the supply of blood, to make the whole course of an inflammation proceed more slowly. This is theoretically quite conceivable, for the quantity of inflammatory products really depends on the quantity of blood flowing through the changed vessels. If this does not exceed a certain amount, then the rapidity of the lymph stream, considerably increased as it is in acute inflammation, may suffice to remove so large a portion of the exudation that the mechanical hindrance to the circulation, produced by the pressure of the effusion on the vessels ramifying in the inflamed tissues, becomes less.

One can, by removing a part of the tissue fluid, facilitate the circulation of the blood. A local withdrawal of blood by wet cupping or leeches will effect this. In special diseases, incisions in the affected part itself are preferred; this is advisable, according to Schröder,[1] in chronic metritis.

But very often, avoiding a direct division of the inflamed tissue itself, we hope, by the removal of a corresponding quantity of blood from the neighbourhood, to effect a diminution of the quantity of blood at the seat of the inflammation; but this appears to me by no means quite certainly established.

It may, however, be possible, by an increased flow of blood to the place at which the vessels are being artificially emptied, that sometimes others in the neighbourhood which communicate with them will be disburdened; but it remains uncertain how long the change in the distribution of the blood will last. From a simply physical point of view, it appears to me that it is incomprehensible why, after the bleeding vessel has again been closed, the former conditions of distribution should not be restored; for the diameter of the vessels, severed by the incision and afterwards closed with thrombi, is too small to admit of any material change being effected in the circulation of the affected part by the exclusion of these vessels. If, therefore, an effect is observed which lasts longer than the special act of blood abstraction, we must think of other factors. First of all the nerves of the vessels should be considered. It is quite conceivable that these would be capable of producing a considerable diminution of the quantity of blood in the affected part. Valid proofs, however, that such is actually the case are not at present to be procured. With respect to the cupping instrument, for example, we might refer to the not inconsiderable amount of mechanical irritation which takes place when it is used, and which might be quite capable of producing reflex effects. We might call to mind that often no removal of blood at all is needed to attain what is wanted, as by dry cupping. Finally, we might put forward the statement that even after dry cupping a tolerably extensive hyperæmic surface shows itself for a considerable time. Supposing that the inflamed

[1] Ziemssen's *Handbuch*, vol. x. art. 'Chron. Metritis.'

part freely communicates with such a surface, and is not too large, a considerable portion of the blood formerly belonging to this part might flow into the relaxed vessels of the hyperæmic surface.

But everything will appear unsatisfactory so soon as other forms of local blood-letting are also taken into consideration. Leeches, in their possible action on remotely situated vessels, or with regard to local blood abstraction, can hardly be considered equal to cupping. The territory acted on by the leech while doing its work is comparatively small so far as its surface is concerned; and after the leech has ceased to draw blood there is little difference between the puncture caused by its bite and one incision of the cupping instrument.

But enough—experiments are wanting, and the subject is too complicated to be unravelled *a priori.*

It is by no means empirically certain that local blood abstraction is generally the proper treatment for inflammation. In gynæcology and ophthalmology a tolerably extensive use is made of it; the surgery of the present day, as it appears to me, has been compelled considerably to limit its use. As I have no personal experience on this subject, I can only refer to the text-books of this branch of medicine. Internal medicine follows quite the same way as surgery. Every physician keeps in reserve a number of circumstances which seem to him to make local blood-letting necessary; it is a matter of individual opinion, and for each person more a matter of faith than of knowledge, and, therefore, it is not subject to criticism. In *meningitis* it is the universal practice to draw blood by leeches; it is also done in *acute peritonitis*, more frequently still in *pleurisy*, accompanied by violent pain, no matter whether this is idiopathic or associated with pneumonia, &c. Here the opiuion of oue stands in opposition to that of another. For my own part I am perhaps too chary of drawing blood, and therefore I keep back my own ideas on the subject. I have never seen a decisive influence result from these blood-lettings, though relief of local pain has pretty frequently followed. They will cause real injury only when one forgets that a somewhat strong local withdrawal of blood is at the same time a general one and acts as such.

Whoever keeps in view the statement, which will hereafter

be laid down, that every withdrawal of blood signifies in itself a loss of body substance will give the preference to a more discriminating treatment.

We come now to the second group—viz. *those methods which are intended to influence the circulation indirectly through the instrumentality of the nerves.* This treatment, as is known, was much more extensively used formerly than it now is. '*Derivation*' was the regularly returning duty of the physician who was called to treat inflammation. The facts more intimately known will find their place in another part of this work. The use of *electricity*, which has, in fact, proved a very important remedy in many cases of inflammation, will also be discussed by itself. Finally, since *the action of different temperatures on the local circulation* falls to Prof. Liebermeister, it only remains for me in this place to refer to what he has written. The usual *medicines* for inflammation must, on the other hand, be discussed somewhat more particularly. We separate most simply those to which a general effect is attributed from those which are thought to act locally.

We take up the former in the first place.

One of the best remedies in inflammation for the changes which usually appear in the blood itself was considered to be *nitrate of potash.* It was extolled as being 'by itself quite capable of removing, to a considerable degree, the inflammatory fever, at the same time as having the power of taking from the blood its strong tendency to coagulate, and of destroying the *fibra sanguinis.*'[1] We know now that the effect of nitrate of potash on bodily heat and circulation, in the usual medicinal doses (1 oz. to, at most, $1\frac{1}{2}$ oz. per day), is scarcely perceptible, and that large quantities of the salt are capable of causing severe gastritis, and eventually even of producing the poisonous symptoms of the potassium salts. It will never be possible to introduce such a quantity of nitrate of potash into the blood as that an appreciable solvent action can be exercised by it on coagulated fibrin: for this purpose about 10 per cent. would be necessary. As little can it be shown that the formation of fibrinogen in the living circulating blood is prevented

[1] Vide Richter, *Spec. Ther.*, i. 140.

by the administration of saltpetre.[1] From all this it results that nitrate of potash does not in any direction fulfil the demands made upon it; that, on the contrary, it may be directly injurious if given in larger doses; and that, therefore, it ought not to be used.

Mercury and its preparations have for a longer period, especially in England, been considered important antiphlogistic remedies. Mercury was extolled as being useful for many things, but on examining the question more closely, we find that all this was nothing more than a means of masking ignorance of its actual effect by a number of forms of expression, such as antiplastic, deobstruent, &c. It was positively maintained of *mercurius dulcis*, i.e. calomel, that it possesses the power of destroying the fibrin of the blood, and, therefore, in a certain degree, of diluting and taking from it its strong tendency to coagulate.[2] Afterwards, mercurialisation in inflammations with a violent commencement, particularly of the serous membranes, became quite the rule in therapeutics, which was in complete opposition to the practice of the earlier physicians, who, like Richter, never used mercury when treating inflammatory fever at the beginning, even when accompanied by exudation. The bad effects of mercurial poisoning are well known. Thorough theoretic researches have also discovered that it has not even the shadow of any possible effect in inflammation. We ought to be very thankful that among practitioners the superstitious belief in the antiphlogistic action of preparations of mercury is more and more disappearing. I have seen a great number of cases of diphtheria and of croup treated by Bartels from the beginning with large doses of mercury *lege artis*, and at the same time I have treated the patients of my polyclinic without mercury; the result was equally bad with both sets of patients. Nor did I succeed any better in discovering any effect which could be regarded as a cure in the case of patients suffering from inflammation, with a violent course and affecting the serous membranes, who, according to the rule, had been mercurialised from the beginning. Others also have not been brought by their observations at the bedside to recognise

[1] See Nothnagel-Rossbach, *Arzneimittellehre*, p. 44.

[2] Richter, loc. cit. p. 148.

mercurius triumphator; thus Nothnagel,[1] in the last edition of his manual, erases mercury quite out of the treatment of inflammatory diseases. It is certainly to the advantage of patients that this remedy should be quite excluded from the therapeutics of inflammatory diseases not caused by syphilis. It would only be tiresome were we at present to consider medicines which are now less generally in use—antimonial preparations, &c. What has just been said will serve *mutatis mutandis* also for them.

The *local antiphlogistic action of medicines* can be judged from various points of view. As for mercury and iodine, in the form of blue ointment, tincture of iodine, and perhaps also ointment of iodide of potassium, we are disposed, on the whole, to admit that they exercise a local action against inflammations; but we are more and more inclined to class them among the counter-irritants. At all events, it must be admitted that these remedies are capable of producing genuine inflammation of the skin, and of stimulating the sensory nerves wherever they come in contact with them. Of the practical value of this kind of revulsion there are various opinions, and it must remain undecided.

The *astringents* next come under consideration. Their activity is confined to the surface of the inflamed skin or mucous membrane; and there can scarcely be a doubt that, coming into contact with this in sufficient concentration, they are capable of acting on the circulation of the blood. The manner of their action, however, is by no means easily comprehended. Chemical processes (coagulation of albumen, &c.) unite with mechanical processes (changes in the elasticity of the tissues, &c., with excitation of the nerves), so that deeper penetration is rendered very difficult. Properly speaking, the subject is not intimately known, and if any physician tries particular remedies he will often obtain surprising results. I need refer only to the researches of Rosenstirn and Rossbach, which proved that tannin does not produce a *contraction*, but the exact opposite, a *dilatation*, of the blood vessels. Theoretically, therefore, there is little to be said about all this group of remedies,

[1] Loc. cit. pp. 122–3.

and even the experience of practitioners appears to me by *no* means conclusive. For my own part, I have never been able to convince myself of the usefulness of astringents—in diarrhœa, for instance—and I very rarely use them; others are of a different opinion. The subject is yet *sub judice*, and much depends on the form of application, which has hitherto been little attended to. A more accurate discrimination must also be exercised in the choice of astringent remedies, which physicians are accustomed to apply, merely changing the medicines according to the systematic classification, but without special grounds for the choice.

Salts of quinine prevent the emigration of the white blood corpuscles through the walls of the vessels and paralyse the corpuscles (Binz). Theoretically considered, it is, therefore, possible that these salts, locally applied, might, to a certain extent, act antiphlogistically. The theory at present, however, is different from what it was when physicians shared the opinion of Cohnheim, that the emigration of these corpuscles is brought about by their power of active movement. We must now remember that other important factors must be taken into consideration, which, however, are almost entirely unknown. This is not the place to discuss possibilities, especially as observations on the practical value of salts of quinine do not lie before us in sufficient numbers for our purpose.

BLOOD-LETTING.

No part of medicine has undergone such great changes as the subject of venesection. For many centuries blood-letting was considered the most active remedy we possessed, and, in many cases, the only one which could preserve life It mattered not whether the pathology of the methodists (*Methodiker*), or the humoral pathology of the dogmatists, was dominant, whether a contraction of the pores, or a dyscrasia of the cardinal juices, was regarded as the cause of disease : blood must always be drawn.

Very few ventured to oppose the practice of venesection, and whoever did so was proscribed, however superior he might be in other respects to the multitude. Erasistratus, Van Helmont—one only requires to hear Galen's opinion of the former and Van Swieten's of the latter.

With scholastic medicine the people held venesection in high estimation : the clergy were foremost. Among many ecclesiastical orders frequent blood-lettings were enjoined as a means of stifling evil desires. If the operation was performed under the right celestial signs—for astrology had a voice in the matter—then many beneficial effects followed : strengthening of the mind, sharpening of the memory, refinement of the senses, a clear voice, a healthy stomach. The powerful remedy was almost universally extolled, and it continued to be practised with undiminished vigour from generation to generation. The last ten years have, however, effected a change. It must appear almost fabulous to those of modern times that even in the fortieth year of the present century official proceedings were possible against a Rhenish physician because he had not bled a pneumonic patient of fifty-six years of age ;[1] for the

[1] S. Kalisch, *Medicinisch-Gerichtliche Gutachten der Königl. Preussisch. wissenschaftlich. Deputation f. d. Medicinalwesen*, in the years 1840–1850, Kirschgässer's Case, p. 98 et seq.

revulsion of feeling has been so strong, at least in Germany, that many in our universities have scarcely an opportunity of seeing venesection practised even once. The people, too, in many districts have no longer recourse to blood-letting ; among the older physicians there are, so far as one individual can judge, very few who now stand up for the heroic remedy of their youth to any considerable extent. At all events, a limit to the indications of blood-letting, such as never existed before, has now made its way among cultivated nations.

For my part, I have never of my own accord practised blood-letting for the purpose of effecting a cure ; and what I have seen of it has been incapable of leaving any doubt in my mind that this treatment is seldom, perhaps never, imperative. Thus I proceed to the questions that are to be discussed here with a certain amount of diffidence. He to whom the history of medicine is something more than a continuous record of human errors will be unable to keep down a feeling of dissatisfaction when he approaches the doctrine of blood-letting. Is there really no germ of truth in the tradition of more than two thousand years ? I believe the question must be asked, but an exhaustive answer cannot yet be given. Why it cannot, becomes clear so soon as the methods of examination that naturally occur are tested by their application to a given case.

The statistical method can, of course, only be used in so far as it is of importance in judging of the desirability of general blood-letting in certain diseases.

The general defect of the method, which consists in this, that it must reckon with relative instead of absolute units, will be felt in a high degree ; and it can only be remedied by bringing forward a large number of figures. If the subject to be considered is the influence which a drug has on a disease, then this drug, in an overwhelming majority of cases, is to be brought forward in addition as an absolute unit. It may be asked, how does a dose of *a* grammes of salicylic acid act, in acute articular rheumatism, on a kilogramme of the body weight ? But, strictly taken, it cannot be asked, how does a blood-letting of *b* grammes act on a kilogramme of the body weight ? For, even though the quantity of the blood and the body weight maintain an almost constant proportion to each other, the

composition of the former varies within wide limits. There is therefore no security whatever given that, with the same weight of blood which was drawn per kilo. of body weight, the same quantity of active material in a number of cases has every time been removed. This factor, therefore, is not to be held as constant.

Still further, drugs have a determinable duration of action; after the lapse of a certain space of time they leave the body. Blood-letting results in a loss to the body, which must be made good. An equal period of time for this replacement cannot be taken for granted; thin people are acted on in a different manner from fat people, young from old, men from women.

It follows from all this that *the lessening of the quantity of the blood may have an extremely varying effect.* The statistical method has, therefore, to do with data which present a very perceptible uncertainty.

There remains a way, which, under all circumstances, permits *a priori* deeper penetration into the matter. First of all, we must determine what effect the lessening of the quantity of blood has upon the body. The more accurately this is known in all its bearings, the easier will it be to answer the question whether, in an individual case, this diminution can be of use when, from any cause, a deviation from the normal has taken place. If such a deviation is clearly surveyed in all its consequences, and if, at the same time, the influence of blood-letting is understood in all directions, then what remains to be considered is scarcely anything more than perhaps a somewhat complicated calculation. The farther we are removed from the actual knowledge of these two data, so much the more uncertain will the result of the calculation be; so much the more must we be satisfied with a proximate estimation. And however far experimental investigation may have gone in this department, there still remain a multitude of unsolved questions, which make it incumbent on us to be cautious in many respects.

The first part of my task consists in the description and explanation of the results which follow a diminution of the quantity of blood.

The immediate effect of a moderate blood-letting is not unpleasant to perfectly strong and healthy people. A feeling of

relaxation and ease will follow almost immediately; somewhat later, slight lassitude and an inclination to sleep, which is described as gentle and refreshing. Such are the accounts handed down from the time in which custom permitted blood-letting, received, too, from unprejudiced physicians.[1] We may feel convinced, in fact, of the correctness of the description in the case of perfectly sound and strong persons. From such subjects I have, in order to procure blood for transfusion, been able to take, at one time, 500 to 600 c.cm., without bad results, either during the operation or afterwards. I sought out for this object the strongest and most muscular vine dressers: I paid them well, so that for several days they were not compelled to work; these at least found themselves in such a condition that neither their work nor their pleasure was disturbed after such losses of blood. It is quite otherwise when weaker people are bled, or when the amount allowed to be taken from one individual is exceeded. From Marshall Hall, who wrote his classical book on blood-letting[2] during the prevalence of a 'frightful vampirism' (Kussmaul), we have received particular descriptions of what, at that time, could be seen every day in the individual bled. I may be allowed to borrow from this reliable source what, in our time, comes under the observer's notice only in pathological conditions, and through these conditions is seen less clearly.

Having mentioned *syncope* as the usual effect of a loss of blood, Marshall Hall thus describes the symptoms during venesection under these circumstances:—

'The patient experiences first a degree of giddiness, to which loss of consciousness succeeds. The respiration is interrupted, and after a somewhat long continuance of the interruption a peculiar painful sensation rouses the patient to breathe deeply and with repeated sighing, and then there again ensues an interruption; the heart-beat and the pulse are slow and weak; the face and general surface become pale, cool, and bedewed with perspiration; at times eructation and vomiting ensue. On recovery there is perhaps a momentary delirium, and, after some yawning, consciousness returns; the breathing

[1] See Schneider, *Die Hämatomanie des ersten Viertels des neunzehnten Jahrhunderts, oder der Aderlass u.s.w.*, p. 237. Tübingen, Laupp, 1827.

[2] *On Blood-letting.*

is at first irregular and sighing, and the pulse gradually becomes normal.

'In cases of *profuse hæmorrhage* other symptoms are manifest; the patient is at one moment more or less syncopic, then he recovers somewhat. During the syncope the countenance is extremely pale; there is more or less insensibility; the respiratory movements are at one time imperceptible, then irregular and sighing; the pulse is slow, feeble, or scarcely palpable; the extremities are cold. Nausea is often felt: if it comes to vomiting, this gives at least temporary relief. In cases of hæmorrhage which terminate fatally, the countenance becomes more pale and sunken, the breathing becomes stertorous and wheezing, the pulse more and more feeble, the extremities colder. Consciousness may be maintained, and the voice remain strong. The patient is affected with constant restlessness and jactitation; impairment of the senses ensues—often delirium, at other times coma.'

The more *remote effects* of a large loss of blood are summed up by Marshall Hall under the general name of 'Exhaustion.' This varies in character in different cases. It may be associated with 'excessive' or 'defective' *reaction*, or with real loss of vital power.

Excessive reaction is developed generally after slow but severe hæmorrhage, and that gradually. At first there is violent pulsation of the arteries, particularly of the carotids; throbbing in the head and palpitation of the heart become very strong. Every bodily or mental excitement aggravates these symptoms. In a higher degree of reaction there is an excessive excitability of the brain, and intolerance of light; every sound, every disturbance in the vicinity increases the already violent pain in the head; straw must be strewn on the streets; the doors noiselessly opened and shut; and, if possible, even the church bells must be silenced. Sleep is restless and disturbed by frightful dreams, so that the patient often wakes out of it in a state of terror approaching delirium. Delusions are not wanting, and the patient fancies he hears singing, the raging of a storm, or the fall of a cataract; at the same time he sees flashes of light and has many other subjective delusive visions: there is a feeling of strong pressure on the head or round it, as

if the head were bound with an iron hoop or bored into by an iron nail; there is deep depression and forebodings of death; the desire for fresh air is very strong; the opening of the windows is desired; a fan is wanted, &c. There are strong and frequent palpitations of the heart, bounding pulse, more rapid respiration combined with sighing and gasping; the skin often seems to be hot.

Defective reaction is most frequently met with among children or old and weak people. It occurs, however, also among strong people who have been frequently bled.

The patient remains for a long time pale and thin; he feels faint on the slightest occasion, is very sleepy and easily frightened. Pulsation of the arteries is not noticeable; the activity of the heart is weak and irregular.

Exhaustion with sinking may be directly united with this condition. The patient is no longer excited by noises as before, the inclination to sleep increases, and the patient on awaking requires some time to recollect himself; he has perhaps quiet delirium, takes notice neither of his own condition nor of the objects surrounding him, and sinks readily again into slumber. A peculiar change takes place in the respiration: a slight rattling is heard, at first audible only to a practised ear; the alæ of the nose are in full play; a desire for air, even during sleep, manifests itself, combined with fits of coughing and accompanied by singular gasping—tympanitis—along with dyspepsia and imperfect closure of the sphincters. The end is denoted by a pale and sunken countenance, restlessness, delirium, coldness of the surface, particularly of the extremities.

Still more vivid is the description given by Schneider of the conditions which were observed after bleeding. This is not the place to repeat his words, but I will extract something of what he has said on the change of nutrition after bleeding. Corpulency often appeared in those who, indulging in idleness and luxurious living, had themselves frequently bled to a small amount, as a means of preventing apoplexy. The examples of this to be found in literature are manifold. Van Swieten remembers a woman who, in the course of a year, had herself bled more than sixty times, in consequence of which she became so stout that in the course of a few months (?) she had gained above

150 pounds in weight. Schneider relates of his own father, a physician, that, in spite of a very active life, he became, by too frequent small blood-lettings, 'fat almost to bursting;' and a year before his death he felt such an overpowering inclination to sleep as to be unable to keep awake for more than five or ten minutes, whether walking, sitting, standing, or riding. Very interesting, too, is a notice, borrowed from Lister, that in England calves are made so extremely fat by frequent bleeding 'that at last the whole mass of their blood is changed into white milky juice.'

In what manner bleeding was practised in the twentieth year of our own century will be shown by one example. I despair of being able to give the graphic description of Audin-Rouvière.[1] If one may trust his word, 1,800 leeches are said to have been applied to a man during one illness. I content myself with communicating the history of one of Marshall Hall's patients.[2] A man of forty years of age, of good constitution, 'a highly esteemed colleague,' fell with his horse, and sustained a fracture of the third and fourth ribs on the left side. Besides violent pain at the seat of the fracture, the pulse was 100 and strong; there was nothing else of importance. Prescription: abstraction of 16 oz. of blood, 12 leeches to be applied to the temples (there was contusion of the face) and to the seat of the fracture, calomel, and purgatives. In the afternoon, it is not evident why, 16 oz. of blood were again drawn. 'During the whole of the second day the patient appeared well, but during the night he was seized with violent pain in the side, which induced him to prescribe venesection for himself. Blood was removed until syncope ensued; and as the blood was received in a wash-basin, the quantity could not with certainty be determined, but appeared to be very considerable. Seventeen leeches were also applied to the injured side, by which the patient was much relieved.' On the morning of the third day after the accident violent breathlessness, combined with pain, was present; and before the physician arrived the patient had caused, first 16 oz., and afterwards 8 oz. more blood to be drawn, which was followed by syncope and relief from pain. On the fourth day

[1] *Plus de Sangsues.* Paris, 1827. [2] Loc. cit. p. 23 et seq.

a cupful of blood; and as in the evening the pain became more violent, 17 oz. were again withdrawn.

The total loss of blood at the end of the fourth day is estimated by Marshall Hall at 120 oz.

From the fourth to the ninth day no further bleeding. Marshall Hall has recorded his veto against the view of his 'excellent colleague,' because all the signs of exhaustion, with excessive reaction, were visible. On the sixth day salivation had set in, showing that the mercury had produced its physiological action.

On the ninth day, after a consultation, wet cupping was ordered, in spite of the opposition of Marshall Hall, who observed threatening symptoms of exhaustion—it is not said to what extent. Aggravation of the symptoms followed immediately, and, in spite of the application of strong stimulants, on the following night death ensued.

At the post-mortem examination the pleura in the vicinity of the fracture was found to be diffusely reddened, but not injured; in the pleural cavity there was a small quantity of lymph; the right lung was bound to the pleura by old adhesions.

This was all; no commentary is needed.

The whole action of blood-letting has been analysed in its details by investigations essentially belonging to the later decades of the century, and has by these been made capable of being in some measure understood.

One of the most important results is that obtained by Worm-Müller[1] and Lesser.[2]

The vascular system has, within wide limits, the capability of adapting itself to a quantity of blood, varying in its amount, so that, after temporary fluctuations, the pressure of the blood in the main arterial trunks remains nearly constant.

Worm-Müller distinguishes three different 'territories,' as he calls them, thus:—

[1] 'Dependence of Arterial Pressure on the Quantity of the Blood,' *Berichte über die Verhandlungen der Königl. Sächs. Gesellschaft der Wissenschaften zu Leipzig*, Mathematical and Physical Class, vol. 25, 1873; *Transfusion and Plethora*, Christiania, 1875.

[2] 'On the Adaptation of the Vessels to Large Quantities of Blood,' also the *Berichte*, vol. 26, 1874.

1st. An anæmic territory. This begins with the highest degree of depletion, admitting of the continuance of life, and extends to an emptying of the vascular system, in which the quantity of blood is diminished by about 1·5 to 2·5 per cent. of body weight; about 20 to 30 per cent. of the normal quantity of blood.

Within the limits which merely admit of the continuance of life the blood pressure in the carotids measures 25 to 35 mm. of mercury; it rises with the increase of the quantity of blood to 120 to 130 mm.

2nd. A middle territory, which begins with an amount of blood of about 1·5 to 2·5 per cent. of body weight below the normal and extends to an amount of blood of about 2 to 4 per cent. of body weight above the normal; fluctuations of about 25 per cent. of the quantity of blood below the normal to 50 per cent. above it.

The increase of pressure does not go parallel with the increasing quantity; it cannot even be always directly recognised. All experiments being summed up, an increase of 120 to 175 mm. in the pressure in the carotids may be noticed.

3rd. A territory which begins with an amount of blood of 2 to 4 per cent. of body weight—about 30 to 50 per cent. of the total quantity of blood—above the normal, and which at its other extreme exceeds the normal by at least 154 per cent. of the original quantity of blood. The pressure in the carotids remains on the whole unchanged. For the physician this last territory of over-filling is of little import. Of the greatest consequence, however, is the fact that changes in the quantity of the blood to the amount of three-quarters of the normal quantity may be rectified by the adaptation of the vascular system, and only proportionally small changes of pressure may ensue.

How this happens is known at least in its principal features. First there comes before us the vaso-motor nervous system, controlling the non-striated muscles of the arteries. If the quantity of blood diminishes, there ensues a contraction of the smaller arteries extending over certain portions of the vascular system. The resistance to the flow of blood being thus increased is sufficient, even after great loss of blood, to maintain the pressure in the larger arteries at a height at which life continues to exist.

It is otherwise when the quantity of blood increases. Then the connections between the arterial trunks and the veins, so far as they are controlled by nerves, open to the uttermost. The flow of the blood into the wide and receptive system of veins is thus facilitated; the arteries are so far disburdened that the pressure in them does not much exceed the normal.

Whether the smaller arteries participate in these changes is not decided. Worm Müller holds that such is conceivable: 'When the quantity of blood increases, the smaller arteries are stretched by the streaming in of the blood, which cannot immediately flow away; in consequence of this increased stretching the muscles of these arteries may possibly be directly stimulated; the small arteries now strive, as it were, like a second heart to drive out the excess of blood.'

For the first and second territories these compensatory arrangements are amply sufficient. But if the quantity of the injected blood exceeds a certain degree—which, however, may be imagined different in different individuals, but must be essentially determined by the time within which the injection takes place—then a physical condition is added to a physiological one. There is, viz., a *stretching of the vascular wall beyond the limits of its elasticity, which is connected with a loss of elasticity.* The vessels immoderately stretched do not return to their normal calibre even when the over-filling ceases. Thus it is impossible to again entirely withdraw from an animal, without endangering its life, the blood which has been injected into it in excess of the full normal amount. In this case, during the withdrawal of blood, at a time when not even the half of the blood which has been introduced above the normal amount has flowed away, the pressure in the carotids sinks far beneath the height which it reached before the beginning of the introduction of the excess of blood, and soon sinks so much that a continuance of life becomes impossible.

Other conditions which could explain such a state of affairs—enfeeblement of the heart's action, diminution or even extinction of the excitability of the muscular system of the vessels, large extravasations of blood internally—are excluded.

The dilatation takes place mostly in the capillaries and smaller veins in the cavity of the chest, and particularly of the

abdomen; the skin, the extremities, and the central organs do not really seem to receive any more blood.[1]

It is interesting to bring forward some details of experiments which it is important to know in order to be able to judge of the possible remedial value of blood-letting.

What is the state of the blood pressure, and the rate of the flow of blood, during and immediately after blood-letting?

With the decrease of the quantity of blood the pressure in the carotids at first sinks considerably, but rises, as soon as the flow of blood is interrupted, to the original height.

The rapidity of the flow of blood also diminishes at first, but soon returns to its former rate.

This is at least true of blood-lettings, which amount to about one-third of the total quantity of the blood of the animal.

As an example I may quote an experiment of Worm Müller's:—

Experiment VIII.[2]

Dog of 5,290 grms. Blood withdrawn from the carotid. Each withdrawal = 50 c. cm. (about 12 per cent. of the quantity of blood). Pressure before bleeding between 153 and 130 mm. mercury.

No. of the Depletion (each of 50 C. cm.)	I.	II.	III.	IV.
Pressure at the end of each depletion	57	92	54	49
Difference of pressure immediately before and at the end of each depletion	73	59	77	63
Duration of depletion (50 c. cm. flowed out in seconds)[3]	10	8	11	44
Maximum pressure within the first 20 seconds after each depletion	161	136	99	52
Time of this pressure, reckoning from the end of each depletion (seconds)	8	20	8	10
Pressure immediately before resuming the depletion	151	129	112	48
Diminution of quantity of blood, expressed in percentages of body weight	0·92	1·88	2·82	3·76

[1] See Cohnheim, *Allgemeine Pathologie*, p. 337 et seq., who, relying on experiments of his own, confirms and accepts the observations and conclusions of Worm Müller. It is worthy of remark that Volkmann was led to accept the doctrine of a governing influence of the nervous system on the blood pressure under these conditions (*Hämodynamik*, p. 226 et seq.)

[2] Loc. cit. p. 626.

[3] The rapidity of outflow was a little delayed in the first depletions.

The result of the experiment showed that a withdrawal of blood of about one-third of the whole quantity can be borne without any very great decrease of the pressure in the carotids. A distinct decrease of the pressure only ensues when the blood withdrawn exceeds this amount; at the same time convulsions show that the utmost limit is reached.

The rapidity of the outflow of the blood is during the first three depletions tolerably equal; during the fourth, which goes very near to the limit of life's continuance, it becomes very considerably slower.

Pressure and rapidity have been at one and the same time determined by Volkmann in the following experiment on a dog:—[1]

Dog of 9,100 *Grms.*

Amount of Depletion in Percentage of Body Weight	Blood Pressure in Mm. Mercury	Rapidity of Blood Circulation in Seconds and Millimetres
0	155	280
0·50	144	259
1·16	127	187
2·41	56	88
3·25	30	48

The experiment was carried out to the end without interruption. It shows that with the decrease of the pressure the rapidity of the flow of blood also decreases—a necessity resulting, as is well-known, from general laws.

The rate of the pulse may here in its turn be discussed.

The rate of the pulse, after withdrawal of blood, is subject to great individual changes; but one rule has been laid down and confirmed by observations at the bedside by all investigators who have paid attention to this matter.

With and after the loss of blood the rate of the pulse first of all increases, and only falls when a more considerable quantity of blood has flowed away.

I may quote in proof of this an experiment of Volkmann on a horse;[2] the withdrawal of blood took place from the carotid.

[1] *Hämodynamik*, p. 226. [2] Ibid. p. 197.

Absolute Amount of Blood Lost	Rate of Pulse	Rapidity of Blood Flow in Seconds and Mm.
Grms.		
0	56	431
680	68	383
2,040	64	345
3,400	74	383
5,440	76	431
6,800	100	287
8,160	110	287
9,740	120	287
11,780	160	157
13,820	152	150

The rapidity of the blood flow and the rate of the pulse do not, as might have been anticipated, stand in a simple relation to each other. The blood flowed with a rapidity of 431 mm. for every 56 and 76 pulsations, and with a rapidity of 287 mm. for every 100 and 120 pulsations.

It is an established fact that after loss of blood the regulating apparatus, which has such a very great direct influence in keeping up the pressure in the arteries, and thereby the circulation, is dependent on the nervous system. But along with these there are other powers at work which are effective in the same sense. For these, also, only a short time is sufficient in order that they may begin their activity; even during the blood-letting they make themselves felt. The whole action of these mechanically active factors consists in the *absorption of fluid into the closed vascular system and its mingling with the blood remaining there.*

Experiments show that very soon after blood is withdrawn that which remains circulating through the body becomes thinner; the number of red blood-corpuscles in the unit of space as well as the solid residue of the serum in the unit of weight diminishes. This fact can have but one interpretation. If fluid, free from blood corpuscles, is not added to the contents of the vessels, then the quantity of corpuscles in the unit of space must remain the same. A decrease of these, growing with the loss of blood, admits of no other conclusion than this: that here the blood has become diluted with a corpuscle-free fluid.

The same thing may be said of the lessening of the serum residue. It must, of course, be premised that the decrease is not caused by errors in the experiments.

I give first of all an experiment of Vierordt,[1] carried out according to the method proposed by him, for directly counting the blood corpuscles.

Dog of 6,161 grms. body weight; blood withdrawn from the crural artery till the animal was bled to death (see the following table):—

Number of Depletion	Amount of each Separate Depletion in Grammes	Time when the Depletion was Performed	Investigation was made after the Last Depletion	Number of Corpuscles in 1 Cub. Mm. of Blood (average)
		hr. min.	Min.	Millions
1	4	1 47	0	4,612
2	55·7	1 50	16	4.110
3	68·4	2 7	20	3,737
4	72·5	2 29	19	3,475
5	96·1	2 50	16	3,743
6	20·0	3 8–12	0	3.175
7	27·3	3 15–20	0	2,371

Whilst in the first four specimens of blood, until the blood withdrawn amounted to 3·3 per cent. of body weight—about 44 per cent. of total quantity of blood—the number of blood corpuscles decreased with every withdrawal of blood, with the fifth depletion a slight increase again appears, though more blood was taken at this depletion than at any other. The increase is so considerable as to lie beyond the limits of error. The same thing was formerly observed by Zimmermann in spite of imperfect methods. Vierordt assents to the explanation and interpretation given by Zimmermann of the apparently paradoxical fact: 'In consequence of the enfeeblement of the animal the blood stagnates in certain vascular areas, and it is not till later that it can again take part in the general circulation.' In the last two specimens of blood the diminution of the red corpuscles is again quite distinct. As the final result of this series of depletions—carried on till the animal was bled to death, and lasting on the whole for 1 hour 33 minutes, and by which 5·6 per cent. of body weight, or about 75 per cent. of the total blood, was withdrawn—the red corpuscles were found to have decreased in number from 4,612 millions to 2,371 millions per cub. mm. Thus there is for the unit of space a decrease of about 51 per cent. of the original quantity.

[1] 'Beiträge zur Physiologie des Blutes,' *Archiv für physiologische Heilkunde*, vol. xiii. 1854, p. 267.

Vierordt sums up the results of his experiments on different animals of the same species, and shows that the extent of the loss of blood has a most decided influence on the number of blood corpuscles. The amount of the blood withdrawn is expressed in its relation to the body weight, and the number of corpuscles after venesection in percentage values of their normal number, which was, of course, previously determined for each individual animal. Notwithstanding conditions unfavourable for a simple comparison, the following numbers must be regarded as full proof that, with the quantity of blood lost, the number of red corpuscles also decreases.

Rabbit. Number of Experiment	Amount of Blood lost in proportion to Body Weight per 1,000 Parts	Number of Blood-Corpuscles after Loss of Blood, in per Cent. of Normal Number
III.	2·3	99
II.	2·4	98
II.	8·8	96
I.	9·1	84
V.	11·8	68
IV.	18·2	69
II.	23·3	52

I add the numbers obtained in an experiment by Buntzen.[1]

Dog weighing 10,800 grms.

Total withdrawal of blood, 258 grms. from the jugular vein; total duration of the experiment, 10 minutes.

First withdrawal of blood	. .	46·5 Grms.
Second ,, ,,	. .	81·0 ,,
Third ,, ,,	. .	89·0 ,,
Fourth ,, ,,	. .	35·0 ,,

Loss of blood during the preliminary operation directly calculated at 6·6 grms.

1st Withdrawal of Blood 10 Minutes before the 4th	Specific Gravity of the Defibrinated Blood	Solid Constituents of the Defibrinated Blood	Depth of Colour of the Blood according to Welcker Panum	Number of Corpuscles in 1 Cub. mm.
				Millions
1st	1064·6	23·0 per cent.	100	8·86
4th	1063·5	22·8 ,,	97·0–97·2	8·43 about 5 per cent. fewer

[1] *Om Ernaeringens og Blodtabets Indflydelse paa Blodet*, Copenhagen, Hauberg & Co., 1879, p. 56.

Lesser[1] communicates in a recent work experiments which, in certain respects, stand in opposition to those which have hitherto been accepted as accurate.

Lesser finds—

The quantity of hæmoglobin in the blood stream does not decrease continuously and in proportion to the total amount of blood lost. The quantity of hæmoglobin remains normal, or shows temporary changes, until the loss of blood has reached a certain extent, then decreases suddenly and continuously. This happened in the experiments whenever the total loss of blood had reached an amount of 2 to 4·4 per cent., on an average 2·9 per cent., of the body weight. The quantity of hæmoglobin is liable to the same changes in venesection as have been proved blood pressure.

Lesser's experiments extend only to the time immediately succeeding a depletion, performed all at once or with interruptions. This is not the place to go more deeply into the details, extremely interesting in many respects as they are, which seem to prepare the way for a deeper penetration into the *minutiæ* of the mechanism which regulates the circulation.

The serum was also examined in Buntzen's experiment, and it was found that the second portion, with a specific gravity of 1021·8, contained 11·5 per cent. of solids; that the third portion, with a specific gravity of 1021·3, contained 10·1 per cent. of solids.

The diminution of the solids—the dilution of the serum—has already been known for a long time.[2] Davy saw in lambs, which had been bled to death, the specific gravity of the serum fall from 1024 to 1018; in oxen, under similar conditions, it sank from 1027 to 1021. Nasse even found during an experiment on a dog, which lasted 30 minutes, a diminution from 1018·5 to 1012·3. The experiments of Lesser deserve particular notice.[3]

Lesser prevented the flow of the lymph into the blood by

[1] 'On the Distribution of the Red Blood Corpuscles in the Blood Stream,' *Du Bois-Reymond's Archiv für Physiologie*, year 1878, p. 41 et seq.

[2] See Nasse, *Das Blut*, p. 148 et seq. Bonn, Habicht, 1836.

[3] Loc. cit.

ligaturing the thoracic duct in dogs. Notwithstanding this, a dilution of the serum itself was observed when a period of only 20 to 25 seconds intervened between two consecutive depletions.

Within the limits of 2 to 6 per cent. of body weight, to which the depletion amounted, there was manifest an increase of dilution proportionate to the amount of blood withdrawn.

In the following table the results of Lesser's experiments are summarised :—

Percentage Residue :—

In the Serum of the Normal Blood	After a Loss of Blood equivalent to following Percentage of Body Weight			
	2–3 per Cent.	3–4 per Cent.	4–5 per Cent.	5–6 per Cent.
7·39	7·15	—	7·00	6·79
7·40	—	7·23	7·00	6·89
7·75	—	—	—	6·31
7·79	7·51	6·69	—	—
8·18	8·09	7·52	7·08	6·78

How is the dilution of the blood, which has been proved with undoubted certainty by all the experiments, brought about ? or, to express it differently, from what source comes the fluid which is poured into the vascular system ? There is a double way open.

The admission of the lymph can take place more easily as the resisting influences, at least after quick depletion, become less. Cohnheim[1] lays particular stress on this circumstance. That the lymph also is more abundantly formed may be concluded from the investigations of Emminghaus.[2] This writer has shown that *with the disturbance of the balance of the elasticity of the tissues, a new formation of lymph begins.* For with the depletion of the vascular system the pressure in its capillaries sinks, though but for a short time, so considerably that the tension of the fluid contained in the tissues predominates, and a current from them into the vessels must take place ; at the same time the increased formation of lymph begins.

[1] Id. loc. cit. p. 158.

[2] *Ber. üb. d. Verhandlungen d. Königl. Sächs. Gesellsch. d. Wissenschf. z. Leipzig*, vol. xxv., 1873, p. 396 et seq.

But this does not perform the principal part, just as the quicker absorption made possible by the distended digestive tract does not. The indisputable result of Lesser's investigations, that even with complete closure of the lymph channels a rapid dilution of the blood takes place, suggests an immediate reversal of the flow, i.e. the return of the tissue fluid into the blood. The relations to time are proportional in this case. Lesser speaks directly on this point with perfect justice :—'*It appears as if the change in the quantity of water in the blood is completed in a very short time, so far as is possible under given circumstances; so that for similar differences in the loss of blood similar changes in the quantity of water in the serum appear, no matter whether a period of seconds or of an hour intervenes between the two depletions.*' When it is remembered that in the experiments which admitted of this conclusion the lymph stream was interrupted entirely, or to a great extent, *the return of the tissue fluids into the blood must be recognised as the main factor.*

An apparent contradiction perhaps requires explanation, or at least mention. It may be asked how such a return of the circulating fluid is possible while the arterial pressure is maintained in spite of the great loss of blood. To this we may reply that at the end of every depletion the blood pressure is, in fact, very considerably lessened. The times, as they are given in Lesser's experiments, show that at all events an equally important absorption of the fluid is quite conceivable.

It is thus manifest from the results of these various experiments that a *change in the composition of the blood follows the loss of blood.* We will now discuss the nature of this change. It is necessary to analyse the general term 'hydræmia,' i.e. increased proportion of water in the blood, more in detail.

Again, *it is of great importance to notice the time which elapses after the blood-letting*; for it appears that in the living body the processes which restore, complete, and bring back the blood to its former condition very quickly come into existence. This is chiefly noticeable in the red corpuscles.[1]

These do not remain unchanged, as it seems, even in form and size.

[1] See below, p. 214 et seq.

Manassein[1] saw in various animals (leech, mouse, mole, rabbit, hare, hen, and pigeon) the red corpuscles increased in size in the period immediately succeeding the loss of blood; in the rabbit, for example, in the proportion of 100 to 114. He ascribed this to an absorption of water from the more diluted plasma, i.e. to simple imbibition. Buntzen,[2] however, has not been able to certify the fact, at least in dogs.

Thus, in his second experiment, after a loss of blood of about one-fourth of the whole quantity, the diameter of the normal corpuscles was shown to be about 7·41 micro-mm. (average of 50 measurements).

35 minutes after the removal of nearly 25 per cent. of the quantity of blood . . . . = 7·37 micro-mm.
24 hours after the removal of nearly 25 per cent. of the quantity of blood . . . . = 7·20 micro-mm.
48 hours after the removal of nearly 25 per cent. of the quantity of blood . . . . = 7·30 micro-mm.
3 days after the removal of nearly 25 per cent. of the quantity of blood . . . . = 7·25 micro mm.
6 days after the removal of nearly 25 per cent. of the quantity of blood . . . . = 7·20 micro-mm.

In all Buntzen's measurements those red corpuscles whose diameter amounted to about 4 micro-mm. were not reckoned. If these had been taken into account in drawing up the average, then a decided decrease of the diameter of the blood corpuscles generally would be found. For, according to Buntzen, the number of these small corpuscles increases very considerably in the first few days after blood-letting. This increase seems to be directly caused by the amount of blood lost; the more considerable the latter is, so much the greater will be this increase.

Buntzen once found, after a depletion equal to about three-fifths of the whole volume of blood, the number of the normal-sized and of the small corpuscles nearly equal. The period of the increase, too, has not been left unnoticed in the investiga-

[1] *Ueber die Dimensionen der rothen Blutkörperchen unter verschiedenen Einflüssen*, p. 40 et seq., and table xii. p. 55. Tübingen, 1872.
[2] Loc. cit. p. 71 et seq.

tion which has been so excellently carried out. The increase of the small blood corpuscles does not immediately succeed the loss of blood; it follows in one or two days, and disappears gradually but slowly during the period of recovery.

Others (Erb, Tschudnowski) saw, after venesection, isolated larger blood corpuscles, which were regarded by Erb as intermediate forms between red and white.

Nasse and Vierordt remarked that during more copious blood-lettings the red corpuscles in the blood withdrawn towards the end of the depletion were paler; and often, but not always (Vierordt), there is a greater tendency of the red blood corpuscles to run together in the blood which is drawn at this time (Nasse).

Not much is known with regard to the behaviour of the white blood-corpuscles. It is for the most part taken for granted that after more severe losses of blood a considerable increase of these takes place (Henle, Remak, Moleschott). But this is not always the case. Buntzen (Experiment V.), after a loss of about three-fifths of the whole volume of blood, saw no increase whatever of the white corpuscles. The same thing is said by Vierordt:[1] 'It is a striking fact that the number of the colourless corpuscles in the blood, even after severe losses of blood, does not increase immediately at least, or only in a very small degree. It is decidedly false to say that the lymph corpuscles of the blood increase very rapidly after venesection.'

A decided opinion on the subject of the changes which the quantity of the fibrin of the blood undergoes after venesection can only be given with reservation. Since the investigations of Sigmund Mayer,[2] confidence in the reliabilty of our quantitative method is somewhat shaken.

This at least holds good in lesser distinctions; Mayer saw in the same blood, by his double analysis, changes to the amount of 20 per cent. It may be added that in each individual the proportion of fibrin in the blood differs to an extraordinary degree. Mayer found in dogs that the fibrin varied from 0·66 to 3·52 per 1,000.

[1] Loc. cit. p. 273.

[2] *Sitzungsberichte der Wiener Akademie*, Mathemat.-naturwissensch. Classe, vol. lvi. 2, 1867, p. 103 et seq.

Earlier investigations are those of Nasse.[1] These present such important differences, that the general conclusion formerly drawn from them, viz. that the fibrin of the blood is lessened by blood-letting, is by no means sufficiently supported.

We must distinguish between two things—

1st:—the changes in the quantity of the fibrin of blood *drawn all at once, but received in separate portions.*

I give first a few numerical examples from the investigations of Brücke.[2]

Brücke bled a dog to death, removing the blood in five separate portions, and found a decrease of the fibrin proportionate to the progress of the depletion.

Number of Successive Portions of Blood	Quantity of Blood Abstracted	Fibrin in 1,000 Parts	Relative Proportion of Fibrin
	Grms.		
1	102·86	2 24	100
2	139·00	1·99	89
3	154·23	1·77	79
4	190·19	1·61	72
5	120·74	0·68	30

In a further series of experiments, the quantity of fibrin sank from 2·90 per 1,000 in the first portion of blood down to 1·84 per 1,000 in the fourth and last portion.

2nd:—changes in the quantity of fibrin in the blood when a *longer period*, one or several days, *intervenes after the first blood withdrawal.*

Under these conditions the quantity of fibrin *increases* with the time and the loss of blood.

Nasse[3] discovered this fact from his own experiments. For example, he drew blood four times from the jugular vein of a dog, once every other day.

	Number of the Venesection			
	1	2	3	4
Quantity of fibrin per 1,000 parts of blood	3·01	4·22	5·23	5·52
Increase of fibrin above the first quantity	100	140	174	183

[1] Loc. cit. p. 152 et seq. [2] *Virchow's Archiv*, vol. xii. 1857, p. 179.

[3] Loc. cit. p. 156.

This was also the experience of Sigmund Mayer,[1] who drew blood from a dog on the second and eighth day after the first depletion.

I.	II.	III.
2·16 per 1,000	4·12 per 1,000	5·50 per 1,000
100	191	255

My own experience with fasting dogs, from which blood was abstracted in the seventy-second and ninety-sixth hour after they had last taken food, was similar.

Number of Experiment	Amount of Blood withdrawn per Cent. of Body Weight	Fibrin per 1,000		Numerical Proportion of Fibrin
		1st Blood-letting	2nd Blood-letting	
III.	2·5	3·48	4·60	100 132
V.	2·7	1·68	3·07	100 183
VI.	2·6	2·99	5·09	100 170

The *time within which coagulation of the withdrawn blood occurs* is influenced by the venesection in no inconsiderable degree.

If the *depletion is carried on uninterruptedly* until death ensues, then the time of coagulation *is shortened*, though less fibrin is contained in the later portions of blood drawn (Brücke).

The method employed by the younger Vierordt[2] allows a stricter determination of the time than those formerly in use. I therefore give the numbers obtained in an experiment of his on a rabbit.

Original weight of the animal, 2,077 grms. Bled from the crural artery; blood lost in the preliminary operation, 5 c. cm.

1st Depletion, 20 *C. cm.*

First drop at 11 hr. 29 min. . . required for coagulation 12 min.
Last „ at 11 hr. 29·5 min. . „ „ 9 min.

2nd Depletion, 30 *C. cm.*

First drop at 12 hr. 46 min. . . required for coagulation 7 min.
Last „ at 12 hr. 46·5 min . „ „ 6 min.

[1] Loc. cit. p. 109.
[2] *Archiv der Heilkunde*, vol. xix. p. 193 et seq.

3rd Depletion, 25 *C. cm.*

Beginning of experiment 2 hr. 56·5 min.		
One drop at 2 hr. 57 min. . .	required for coagulation	3·5 min.
„ 2 hr. 58 min. . .	„ „	3·0 min.
„ 2 hr. 59·5 min. . .	„ „	2·25 min.

This was one of the last that spontaneously flowed out.

These investigations perfectly coincide in their results with the assertions of Brücke.

Opinions differ with regard to the *period of coagulation when an interval of some days separates the several depletions.* Nasse[1] found in a dog, from the crural vein of which he had on each of four succeeding days drawn about 2 oz. of blood, that coagulation occurred in 60, 67, 77, or 87 seconds; he was of opinion, however, that here considerable differences happen in different cases, and that the amount of blood withdrawn has also an influence.

Regarding *changes in the chemical and physical qualities of the fibrin*, which appear to us of less importance, at least for the present, it is mentioned even in the earlier literature that, after any considerable loss of blood, the blood clot quickly separates from the serum. It is also remarked that after very severe venesection the fibrin in the blood which has been last removed is looser, softer, less elastic, and therefore the contraction of the blood clot is less perfect.

The *composition of the serum* after blood-letting is in its details not very well known.

It has been already mentioned, and is proved by the experiments of Lesser,[2] that *after a venesection performed, with short interruptions, at one sitting, a diminution of the solids quickly takes place*, and therefore an increase in the proportion of water occurs.

I have made a considerable number of experiments on dogs, in which *a longer time elapsed between the consecutive depletions*, and the following is the result:—

[1] Loc. cit. p. 135. [2] See above, p. 177.

Number of the Experiment	Hour of Fasting	Amount of Blood withdrawn in per Cent. of Body Weight	Solid Constituents of the Serum, per 1,000	Specific Gravity of the Serum
III.	72	2·5	75·4	1028·4
	96		75·5	1027·0
IV.	72	1·3	103·6	1031·6
	96		102·3	1030·8
V.	72	2·7	86·8	1025·7
	96		77·3	1024·4
VI.	72	2·6	89·6	1026·7
	96		84·5	1026·1
VII.	72	1·5	80·8	1025·4
	96		78·9	1020·3
IX.	72	3·4	85·7	1026·1
	96		79·4	1023·8
XV.	72	2·2	83·5	1034·5
	96		80·3	1031·2

In all these experiments twenty-four hours intervened between the first and the second depletion. In the two following the *time of the depletions varied,* but they were also performed on *fasting dogs* :—

Number of the Experiment	Hour of Fasting	Amount of Blood withdrawn per Cent. of Body Weight	Solid Constituents of the Serum, per 1,000	Specific Gravity of the Serum
XIII.	69	2·6	80·7	1030·4
	143	—	77·2	1030·7
XIV.	28	1·8	87·5	1035·0
	100	—	81·5	1033·9

In the next experiment, again performed on fasting dogs, three blood-lettings—in the 72nd, 96th, and 120th hour of fasting—took place.

Number of the Experiment	Hour of Fasting	Amount of Blood withdrawn per Cent. of Body Weight	Solid Constituents of the Serum, per 1,000	Specific Gravity of the Serum
8	72	2·1	89·1	1025·3
	96	0·8	88·8	1025·8
	120	--	87·1	Not determined
10	72	2·7	93·4	1026·4
	96	1·1	89·2	1022·0
	120	—	91·6 (?)	Not determined

In the following experiment the dog was allowed to eat as much as it pleased, and 24 hours intervened between the successive blood-lettings :—

Experiment XII.

Body Weight in Grammes	Amount of Blood withdrawn per Cent. of Body Weight	Solid Constituents of the Serum, per 1,000	Specific Gravity of the Serum
6,980	2·6	81·6	1029·8
7,000	2·1	76·1	1028·8
6,950	—	71·3	1024·6

The numbers just communicated plainly prove that, in the case of fasting dogs at least, an almost constant, although only *slight, change takes place in the serum after blood-letting ; and this in the sense of a diminution of the quantity of solid constituents and an increase in the quantity of water.*

In general, it may be accepted as a fact *that only within very narrow limits changes in the quantity of water in the serum take place.*

My twelfth experiment also corroborates this, since it shows that within two days the original quantity of blood was diminished by about $\frac{3}{5}$ of the whole ; the solid constituents of the blood were reduced from 22·73 to 13·90 per cent. ; and notwithstanding this, the quantity of solid constituents in the serum was found to be but little diminished—about 1 per cent. exactly. If the numbers of this experiment are compared, they are as follows :—

Blood-letting . .	1	2	3
Blood[1] . . .	100	78	50
Serum	100	92	87

Thus it appears that the composition of the serum is but little

[1] Determined from the difference between the solid residues of blood and serum ; see Panum, ' Experimentelle Untersuchungen zur Physiologie und Pathologie der Embolie, Transfusion und Blutmenge ' (Berlin, Reimer, 1864), originally published in *Virchow's Archiv*, vols. xxvii. and xxix. p. 166 et seq. and p. 265 et seq.

changed in the case of a dog which preserves its full weight, and eats as much as it pleases after venesection.

It might be asked still further, *if the composition of the solid residue of the serum* is the same after blood-letting, or if changes take place; for instance, if the proportion of albumen is diminished?

It is at present impossible to assert much that is definite on this subject. The statements of the earlier writers cannot be made use of.[1] Panum[2] makes the communication that perhaps a small decrease of serum-albumen takes place, but he will on no account guarantee the truth of the statement. I have myself twice determined the amount of albumen in fasting dogs; and at one time I found a considerable increase, and at the other time a smaller one.

Thus in Experiment XIV., after a withdrawal of blood equivalent to 1·8 per cent. of the body weight, the quantity of albumen in the serum had risen in 72 hours from 4·87 per cent. to 4·92 per cent. In another experiment (XV.), after a withdrawal of blood of 2·2 per cent. of the body weight, the quantity of albumen, amounting originally to 2·66 per cent., 24 hours later increased to 3·95 per cent.

It appears, however, that scarcely any permanent changes deserving of notice take place. The statements of Becquerel and Rodier,[3] which, however, cannot be followed up in detail, also bear testimony on this subject. These investigators found, with regard to 10 persons who were each three times bled, on an average the following percentage of serum-albumen—

1st Venesection.	2nd.	3rd.
6·5	6·37	6·46

The *ash of the serum* is equally unknown in its changes after blood-letting. According to Becquerel and Rodier a change is not to be expected.

The *alteration of the gases in the blood* after venesection has been followed out in a small series of experiments by Hüfner, who was so kind as to make these investigations with me.

[1] See Nasse, loc. cit. p. 162. [2] Loc. cit. p. 240 et seq.

[3] *Untersuchungen über die Zusammensetzung des Blutes*, p. 39 et seq. Erlangen, Enke, 1845.

In order to have as simple conditions as possible, we chose fasting dogs. The depletions were all from the crural artery or the carotid. The blood was collected over mercury; and, according to the usual method, the gases were removed by means of Hüfner's mercurial pump.

Experiment I.

Dog of 15·9 kilos., after fasting for 67 hours.

First withdrawal of blood of 410 grammes = 2·6 per cent. of the body weight, or about 35 per cent. of the total quantity of blood.

Second withdrawal of blood, 74 hours later.

Gases in the Blood—in 100 Vols. of Blood, at 0° C. and 760 Mm.	First Depletion	Second Depletion
Total quantity	42·98	44·97
Carbonic Acid . . .	29·72	35·02
Oxygen	10·34	8·99
Nitrogen	2·91	0·96

Thus in 100 vols. blood, 74 hours after the first blood-letting, oxygen is decreased by 1·35 vols., and carbonic acid is increased by 5·30 vols.; or, representing the quantity of each gas in the first depletion by 100, the quantity in the second depletion would bear the following proportions to it:—

Oxygen . . . . as 100 to 87
Carbonic acid . . . „ 100 „ 118.

Experiment II.

Dog of 45 kilos., after fasting for 29 hours.

First depletion of 800 grammes = 1·8 per cent. of the body weight, or about 24 per cent. of the total quantity of blood.

Second depletion, 72 hours later.

Gases in the Blood—in 100 Vols. of Blood, at 0° C. and 760 Mm.	First Depletion	Second Depletion
Total quantity	51·03	31·30
Carbonic Acid . . .	25·08	17·04
Oxygen	24·01	12·86
Nitrogen	1·94	1·40

Therefore in 100 vols. of blood we find, 72 hours after the first depletion—

Oxygen . . .	11·15	vols. less
Carbonic acid . .	8·04	„

Or taking the quantity of each gas in the first depletion as 100, then the second bears the following proportion to it, viz.:—

Oxygen	100 to 54
Carbonic acid	100 „ 68.

Experiment III.

Dog of 35·3 kilos., after 49 hours of fasting.

First depletion of 760 grammes = 2·2 per cent. of the body weight, or about 29 per cent. of the total quantity of blood.

Second depletion, 24 hours after the first.

Gases in the Blood—in 100 Vols. of Blood, at 0° C. and 760 Mm.	First Depletion	Second Depletion
Total quantity	37·91	36·68
Carbonic Acid . . .	17·41	19·19
Oxygen	19·62	16·69
Nitrogen	0·88	0·88

Thus, in 100 vols. of blood, 24 hours after the first depletion—

Oxygen	2·93	vols. less
Carbonic acid . . .	1·78	„ more.

Reckoning 100 for the first depletion, we get as the proportion of the first to the second—

Oxygen	100 to 85
Carbonic acid . . .	100 „ 110.

In every experiment the residue of the blood and of the serum, and the specific gravity of both, were determined. A comparative expression for the quantity of red blood-corpuscles can thus be obtained from data so certain.[1] It is not uninteresting to compare these with the results of the analysis of the gases, reckoning the values found at the first depletion as 100.

[1] Panum, loc. cit.; see above, p. 209.

Experiment I.

First blood-letting = 2·6 per cent. of body weight.
Second one, 74 hours afterwards.

Amount of Red Blood Corpuscles		Oxygen	Carbonic Acid
Residue	Specific Gravity		
100 91	100 84	100 87	100 118

Experiment II.

First blood-letting = 1·8 per cent. of body weight.
Second one, 72 hours later.

Amount of Red Blood Corpuscles		Oxygen	Carbonic Acid
Residue	Specific Gravity		
100 91	100 96	100 54	100 68

Experiment III.

First blood-letting = 2·2 per cent. of body weight.
Second one, 24 hours later.

Amount of Red Blood Corpuscles		Oxygen	Carbonic Acid
Residue	Specific Gravity		
100 91	100 92	100 85	100 110

Thus, in every experiment, a diminution of the oxygen has been observed, as appears quite easily comprehensible from the circumstance that a diminution of the hæmoglobin was brought about by the withdrawal of blood. It is, however, extremely

striking that this diminution varies within such wide bounds. Whilst the comparative number of the red blood-corpuscles in all three experiments is nearly the same, the oxygen of the second experiment falls relatively very much below that of the other two. It is difficult to say what is the cause of this. It might, however, be mentioned that in this particular animal a larger quantity of oxygen was found. In order to settle this absolutely, a considerably greater number of experiments must be made.

In the carbonic acid of the blood there is manifested no regularity. It may be noticed that in two of the experiments a not inconsiderable increase took place.

Finkler[1] has made observations on the gases of the blood a short time after depletion. This observer has made an analysis of venous blood directly drawn from the right side of the heart, as also of arterial blood from the femoral.

His final conclusions are:—

With regard to venous blood, there is, along with the loss of blood, a diminution of the percentage of oxygen, and also a diminution of the percentage of carbonic acid.

With regard to arterial blood, the quantity of oxygen it contains does not vary so much, but, on the other hand, there is a diminution of the quantity of carbonic acid.

However, the simple numbers of his experiments are by no means so constant as to seem to justify the latter conclusion without further knowledge; on the contrary, great variations are to be found even under these experimental conditions, as the following table of Finkler's shows (Table C).

It must at the same time be remarked that 'a longer time elapsed (at least one hour) between two venesections, and that in Experiments V. and VI. at the same time as the venous venesection took place an arterial one was also performed.' The total quantity of blood is reckoned at 7·5 per cent. of the body weight.

For further conclusions his experimental data appear to me insufficient.

[1] *Ueber den Einfluss der Strömungsgeschwindigkeit des Blutes auf die thierische Verbrennung*, Dissertation. Bonn, 1875.

TABLE C.[1]

No. of Experiment and of Depletion	Percentage of Blood withdrawn	Quantity of Gas in Venous Blood: Oxygen	Venous Blood: Carbonic Acid	Arterial Blood: Oxygen	Arterial Blood: Carbonic Acid	Remarks
IV. 1.	0·76	12·82	47·10	18·31	3·48	Blood shaken with air
2.	1·46	12·53	45·08	—	—	
3.	2·16	6·48	45·55	—	—	
4.	2·84	4·32	45·85	17·96	33·90	
V. 1.	0·49	11·8	41·49	13·52	33·20	
2.	0·93	8·8	42·03	13·10	36·94	
3.	1·33	4·06	40·31	13·08	32·45	
4.	1·9	2·71	41·49	13·96	35·89	
VI. 1.	0·33	10·96	43·42	16·62	37·30	
2.	1·6	7·59	35·90	15·45	27·43	
3.	2·48	5·98	34·73	—	23·30	

These few facts may be sufficient.

Before the further consequences of blood-letting are discussed, it will be proper to mention here *how the blood becomes restored after blood-letting.*

I consider the results obtained by Buntzen by means of the method of counting the red blood-corpuscles as quite reliable, and I also regard the explanations given by him of the difference between his results and those found by others as quite satisfactory; so that here I simply borrow from Buntzen.[2]

The question, *How long is it after depletion before the quantity of blood contained in the vascular system has returned to its former volume?* is, in accordance with Panum's earlier results, thus answered :—

After losses of blood which amount to 1 or 2 per cent. of the body weight (that is, about $\frac{1}{4}$ of the whole quantity of the blood), the volume of the blood is restored after the lapse of a few hours. If more blood than amounts to 4 per cent. of the body weight is withdrawn, then more than 24 hours must elapse before the volume of the blood reaches its former condition.

The following particulars from Buntzen's experiments are interesting :—

The lowest number of blood corpuscles in a given quantity

[1] Finkler, loc. cit. p. 10.

[2] Loc. cit. p. 61 et seq.

of blood gives us the highest degree of dilution which, after losses of blood, takes place by absorption of water into the vascular system. There was found—

No. of Experiment	Amount of Blood withdrawn per Cent. of the Body Weight	Time of the Greatest Dilution after the Venesection
I.	1·14	$1\frac{3}{4}$ hour
II.	1·98	3 hours
III.	2·39	Later than 2, but in the course of 24 hours
IV.	4·42	After 48 hours

A second very important question is, *How long is it before the number of red corpuscles in the blood after depletion becomes the same as it was before it?*

The general result of experiments showed that, in blood-lettings varying between 1·1 and 4·4 per cent. of the body weight (that is, about 14·8 to 51·5 per cent. of the whole quantity of the blood), from 7 to 34 days were necessary in order to bring about a restoration of the red blood-corpuscles that have been lost.

On the whole, the length of time required appears to be in proportion to the amount of blood lost. But in the separate experiments of Buntzen undoubted differences appeared, which possibly must be ascribed to particular dispositions, perhaps also to the kind of nourishment.

Number of Experiment	Loss of Blood per Cent. of Body Weight	Blood Lost per Cent. of the Total Amount of Blood	Number of the Blood Corpuscles per C. cm. before the Depletion	The Smallest Number of Blood Corpuscles found in 1 C. cm. after the Depletion	Time required for the Restoration of the Blood Corpuscles to Normal Number	Daily Consumption of Food during this Time
			Millions	Millions	Days	
1	1·14	14·8	6·71	5·61	14	400 grms., bread
2	1·98	25·7	7·62	5·91	7	500 „ meat 70 „ bread
3	2·39	31·0	9·02	6·61	15	500 „ meat 70 „ bread
4	2·86	37·2	4·63	3·22	9–10	Milk, meat, and bread
5	4·42	57·5	8·85	3·64	34	500 grms., meat 58 „ bread
Number of the column in the original table	3	4	6	7	12	13

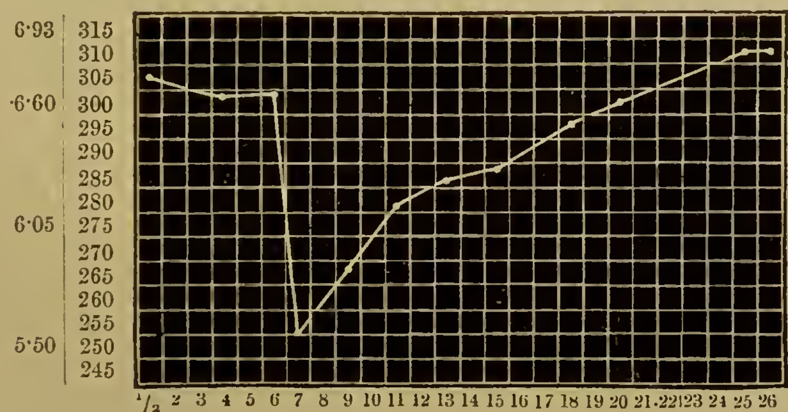
The renewal of the red blood-corpuscles takes place more quickly in the first few days after the loss of blood than later.

It is desirable also for these proportions to give numbers. The preceding is Buntzen's principal table (p. 216).

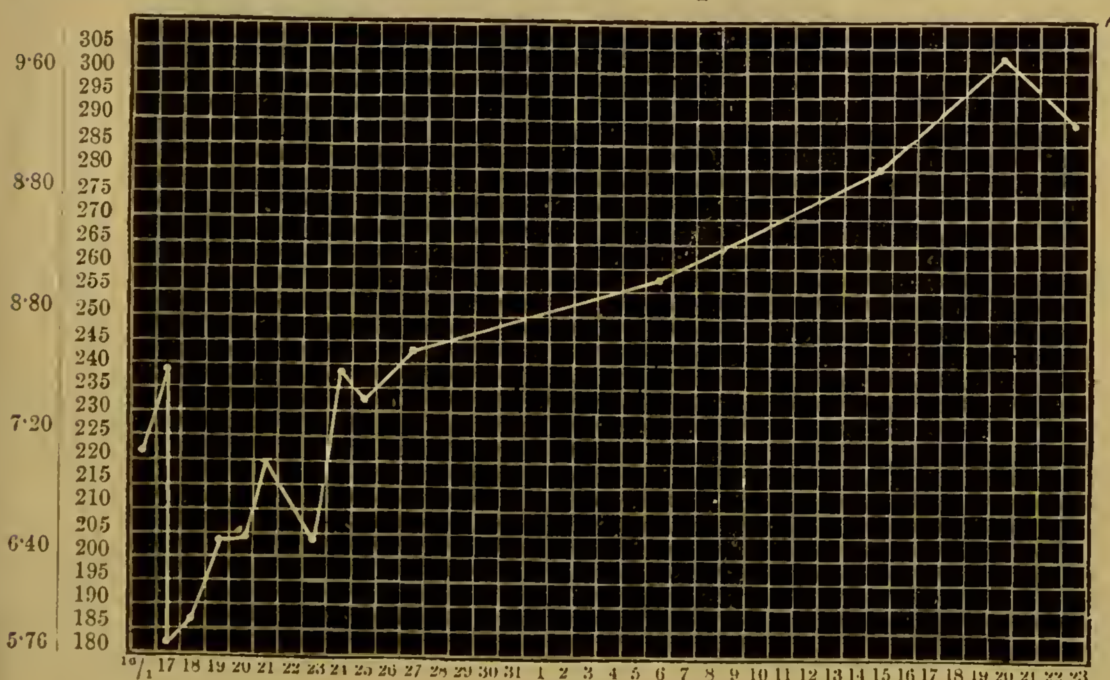
It is also worthy of notice that Experiment IV. was performed on a dog only about six weeks old, and that Experiments II., III., and V. were performed on one and the same dog, with moderate intervals between them.

The time of the restoration of the blood in its individual course is best demonstrated by the following graphic representations borrowed from Buntzen.

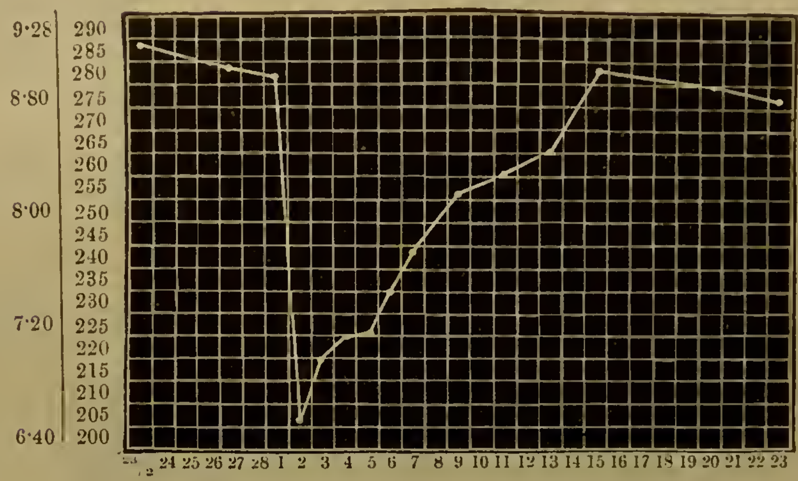
Experiment I. Blood withdrawn = 14·8 per cent. of whole blood.



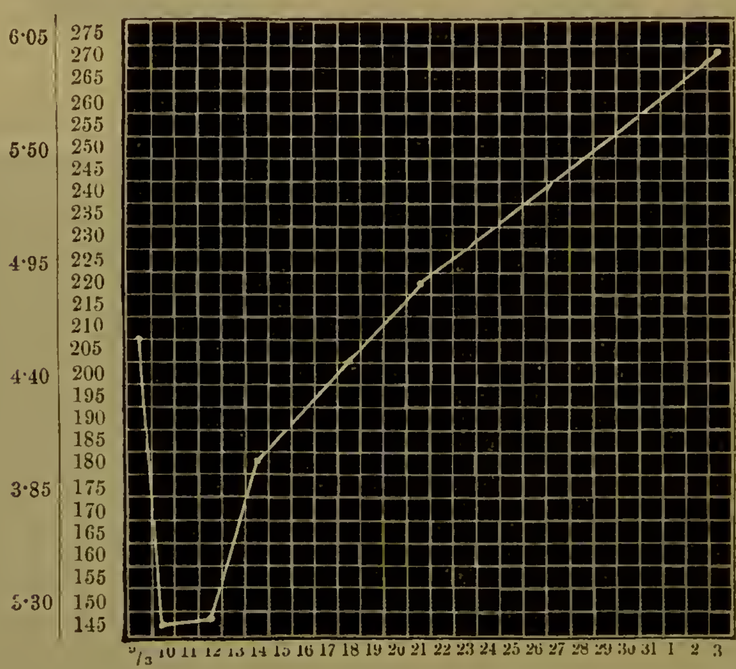
Experiment II. Blood withdrawn = 25·7 per cent. of whole blood.



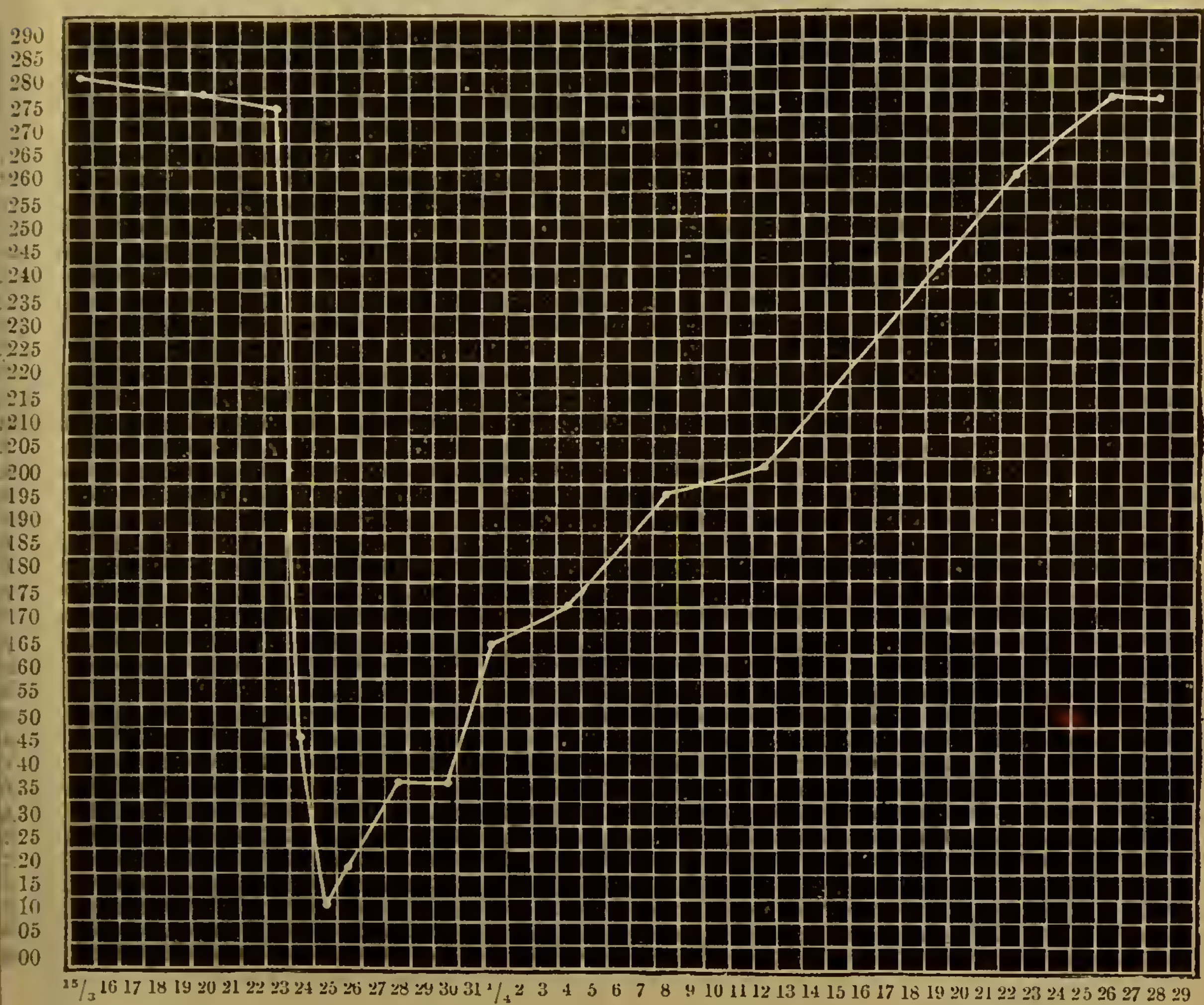
Experiment III. Blood withdrawn = 31 per cent. of the whole blood.



Experiment IV. Blood withdrawn = 37·2 per cent. of the whole blood.



Experiment V. Blood withdrawn = 57·5 per cent. of the whole blood.



The outer vertical row of figures gives in millions the calculated number of blood corpuscles contained in 1 c. mm. of blood; the inner row represents the numbers obtained by direct enumeration of the corpuscles in the quantity of blood examined under the microscope; the under horizontal row gives the day of the experiment.

How far this result of an experiment on a dog may be transferred to man must, as Buntzen justly remarks, be left for further investigation. The difference of species between the two may perhaps weigh heavily here.

We come now to the discussion of the question, *In what way is tissue metamorphosis in general changed after blood-letting?* The results of the investigations lying before us agree, although they appear, at the first glance, somewhat contradictory.

Considering the great importance which this part of the subject possesses, in judging of the therapeutic efficacy of venesection, a thorough treatment of the matter is imperative. I have for a long time devoted my attention to nitrogenous metamorphosis, and have published the smaller part of my experiments in the form of a dissertation.[1]

Bauer, to whom my work remained unknown, which as regards a dissertation is not surprising, obtained the same results, and by careful consideration of the total tissue metamorphosis supplied the material that was wanting.[2]

In fasting animals the proportions come most prominently into view. A very considerable number of experiments which I made on dogs proved—and Bauer's results are similar—that *after blood-letting, in the case of dogs to which all food, water inclusive, is denied, a considerable increase of excretion of urine and urea takes place.*

The manner in which my experiments were made requires mention. After the dogs had fasted for 48 hours, the urine was removed from the bladder by means of the catheter. The animal was placed in a box, which allowed all the urine spontaneously passed to be collected. As a general rule—only isolated exceptions occurred—after 48 hours of fasting no urine was spontaneously passed. That which was formed within 24 hours, and which was retained in the bladder, could, however, after the lapse of this period, be procured to the very last drop. The body weight was determined to within 10 grms. The fæces, which were rarely passed, were weighed. Blood was drawn from the crural artery or the carotid. The small operation had no perceptible influence—this I made certain, as Bauer did, by making control experiments.

As a standard of comparison for the change which takes place in the excretion of urine and urea by the withdrawal of blood, the quantity of each passed by both dogs during the 48th and 72nd hours of fasting was chosen as the unit (*Einheit*). That this is quite allowable under existing conditions seems to admit

[1] *Quomodo Ureæ Excretio Sanguine Exhausto afficiatur.* Kiel, 1863.

[2] 'Ueber die Zersetzungsvorgänge im Thierkörper unter dem Einflusse von Blutentziehungen,' *Habilitationsschrift*, Munich, 1872; and *Zeitschrift für Biologie*, vol. viii. p. 567 et seq.

of no doubt (Panum, Voit, and several other physiologists). The urea was estimated by Liebig's method.

I submit the following table :—

TABLE A.

No. of Experiment	Hours of Fasting	Body Weight at the 72nd Hour of Fasting, before the Depletion	Loss of Weight	Amount of Blood drawn (72nd Hour of Fasting)	Amount of Blood Lost per Cent. of Weight of Body	Amount of Urine	Amount of Urea	Urine per Kilo. Body Weight	Urine Passed in 24 Hours before the Depletion=100	Urea per Kilo. Body Weight	Urea Passed in 24 Hours before the Depletion=100	Loss of Weight per Kilo. of the Total Weight of the Dog
		Grms.	Grms.	Grms.		C. cm.	Grms.	C. cm.		Grms.		Grms.
I.	48–72	3,700	160	44	1·2	55	4·8	14·3	100	1·2	100	41·5
	72–96	—	126	—	—	65	6·1	17·8	125	1·7	135	34·5
II.	48–72	9,400	490	60	0·6	125	15·2	12·6	100	1·5 (4)	100	49·5
	72–96	—	440	—	—	110	13·8	11·8	93	1·5 (48)	96	47·4
III.	48–72	6,760	510	166	2·5	110	14·8	15·1	100	2·0	100	70·2
	72–96	—	444	—	—	180	22·4	27·3	180	3·4	167	67·3
IV.	48–72	11,370	550	150	1·3	140	8·1	11·7	100	0·7	100	46·1
	72–96	—	560	—	—	150	11·6	13·4	114	1·0	151	49·9
V.	48–72	7,390	130	200	2·7	29	2·1	3·9	100	0·3	100	17·3
	72–96	—	240	—	—	95	7·4	13·2	342	1·0	377	33·4
IX.	48–72	3,260	137	110	3·4	40	2·5	11·8	100	0·7	100	40·3
	72–96	—	120	—	—	74	5·6	23·5	200	1·8	243	38·1
XI.	48–72	10,395	230	240	2·3	80	8·0	7·5	100	0·8	100	21·7
	72–96	—	254	—	—	116	11·9	11·4	152	1·2	157	31·5

It is thus demonstrated that *after blood-lettings* which vary between 1·2 and 3·4 per cent. of the body weight, that is, about 15 to 45 per cent. of the whole quantity of the blood, the *urea* excreted in the 24 hours following the blood-letting *increases more than threefold.*

In general, there is a manifest dependence, so that, with the increasing amount of blood withdrawn, the quantity of urea excreted also increases ; a simple parallel proportion, however, does not exist.

This scarcely appears strange when it is considered that here conditions prevail under which two individuals cannot, without some further provisoes, be compared according to their weight of body, and the unit thus procured. Thus the urea excreted on the third day of fasting by a dog of 1 kilo. weight amounts to 0·3 grm. ; that passed by another animal amounted

to 2 grms. Thus the one quantity is more than six times that of the other.

The quantity of the urine is also increased after blood-letting—as a maximum to nearly $3\frac{1}{2}$ times the normal quantity. A similar state of things is recognisable in the excretion of the urine as in that of the urea; both have an entirely similar course.

A blood-letting of 0·6 per cent. of the body weight (about 7 per cent. of the whole quantity of the blood) has no definitely recognisable influence on the excretion of urine and urea.

From the experiments of Bauer it may be remarked, as complementary to what has been said, that the increase in the excretion of urine and urea after blood-letting lasts longer than 24 hours. Apparently it may continue for several days.

Bauer bled a dog which had been kept fasting, first on the 8th, and then on the 11th day of fasting. Blood was withdrawn to the amount of about 1·5 or, at most, 3 per cent. of the body weight. The weight at the beginning was about 20 kilos.; the blood first withdrawn amounted to 256 c. cm., the second time to 400 c. cm. After the first blood-letting there was found, compared with that of the preceding day, an increase, in the quantity of urea excreted, of about 78 per cent. After the second blood-letting there was an increase also above the amount of the preceding day of 37 per cent. The numbers, in detail, are as follows:—

Day of Fasting	Amount of Blood Withdrawn	Amount of Urine Excreted	Amount of Urea Excreted	Comparative Numbers
		C. cm.	Grms.	
7	—	96	6·42	100
8	256 c. cm.	140	11·48	179
9	—	106	10·08	157
				(140)
10	—	86	8·98	100
11	400 c. cm.	122	12·34	137
12	—	101	10·02	112

It is plain from the above table that the second blood-letting does not exceed in its results the previous one. My experiments, particularly directed to this point, bear testimony to the same thing. If, as in Experiment VII., two smaller blood-

TABLE B.

No. of Experiment	Hours of Fasting	Body Weight before the Blood-letting at the 72nd Hour of Fasting	Loss of Weight	Amount of Blood Withdrawn	Amount of Blood Withdrawn per Cent. of Body Weight	Quantity of Urine Excreted	Amount of Urea Excreted	Amount of Phosphoric Acid Excreted	Urine per Kilo. of Body Weight	Urine Excreted in 24 Hours before the Blood-letting = 100	Urea per Kilo. Body Weight	Urea Excreted in 24 Hours before the Blood-letting = 100	Phosphoric Acid per Kilo. of Body Weight	Phosphoric Acid Excreted before the Blood-letting = 100	Loss of Weight per Kilo. of Dog
		Grms.	Grms.	Grms.		Ccm.	Grms.	Grms.	Ccm.		Grms.		Grms.		Grms.
VII.	48–72	5,730	200	72nd hour of fasting 90	1·5	65	3·6	0·41	11·0	100	0·6	100	0·07	100	33·7
	72–96	—	200	96th hour of fasting 57	1·1	78	5·5	0·55	13·8	126	1·0	162	0·10	136	35·5
	96–120	—	163	—	—	53	4·3	0·40	9·9	82	0·8	120	0·07	98	30·2
X.	48–72	9,335	305	72nd hour of fasting 250	2·7	80	6·2	0·37	8·3	100	0·6	100	0·04	100	31·6
	72–96	—	255	96th hour of fasting 100	1·1	108	9·6	1·05	11·9	143	1·1	166	0·12	282	28·1
	96–120	—	202	—	—	94	8·3	0·61	10·8	117	1·0	131	0·05	164	23·1

lettings follow the first, at separate intervals of 24 hours from each other, then, of course, the excretion of urea is greater than it was at the beginning, but not that of the phosphoric acid. The excretion of water is diminished. At all events, a simple summation does not take place. This is proved also by my Experiment X., in which the quantity of these constituents passed on the second day is probably caused in part by the first blood-letting. See Table B, preceding page.

Bauer has investigated the influence of blood-letting on a dog, the normal quantity of whose excreted nitrogen had by a suitable dietary been made constant. I communicate the results of his investigations, and remark that the results of experiments made by me by a less perfect method coincide in the main with his.

Table C.

Day of Experiment	Amount of Urine	Urea	Remarks
	C. cm.	Grms.	
6	450	36·49	
7	444	36·65	
8	513	43·42	Blood withdrawn, 350 to 460 c. cm.
9	534	42·96	
10	512	41·92	
11	449	36·50	

The increase of urine and urea is also here unmistakable. After a blood-letting of about $\frac{1}{4}$ of the whole quantity, the urine, compared with that of the previous day, is found to be in the proportion of 116 to 100, and the urea of 129 to 100. It is true the dog had drunk a great deal of water after the blood-letting, but the increase in the quantity of urine continued during the next two days, although on these days no water was directly administered. Water-drinking, therefore, is no truly governing factor in determining the increase of excretion.

Bauer calculates, according to the well-known equivalents of the Munich Physiological Laboratory, the loss of nitrogen, which was occasioned by the blood-letting during the first four days, at 298 grms. of fresh muscle flesh, in the case of a dog of about 20 kilos. weight. Thus there is a loss of about 1·5 per cent. A small amount of flesh (nitrogen) appeared to have been put

on about the sixth day after the blood-letting and in those following it.

Bauer has also investigated the *decomposition of fats* (the metabolism of nitrogen-free bodies) occurring after depletion.

It was proved that *immediately* after a diminution of the quantity of blood to the extent of about 20 per cent.—that is to say, within the first four hours—in the case of *fasting* dogs, the amount of *carbonic acid* excreted does *not* appear to be altered. On the other hand, the *elimination of water by the skin and lungs*, as well as the *absorption of oxygen*, is *diminished* by about $\frac{1}{6}$. About 20 hours after the operation the excretion of carbonic acid is found to be diminished about 23 per cent., and the absorption of oxygen about 30 per cent.

In dogs that had been *fed*, immediately after blood had been drawn to the amount of about 28 per cent. there was an *increase of the excretion of carbonic acid* to the extent of 4 per cent., and an *increased absorption of oxygen* to the extent of 22 per cent.; such, for the first three hours after the blood-letting, are the direct results of the experiment.

After 24 hours a *distinct decrease* is perceptible, of 9 per cent. of *carbonic acid* and 2 per cent. of *oxygen*. Three days afterwards, this decrease is very considerable, being 22 per cent. of *carbonic acid* and 36 per cent. of *oxygen*.

Bauer draws this general conclusion from his experiments :—

'It is proved that in consequence of blood-letting the decomposition of albumen increases; the elimination of carbonic acid, on the contrary, decreases. From this, therefore, it is clear that the decomposition of fat must be smaller, whether it come from the food, or that which is stored up in the body, or that which results from the breaking up of the albumen.'

This conclusion is supported by other proofs, even for him who hesitates to accept it on account of the inconsiderable number of Bauer's experiments on the respiration. Bauer himself refers to the above-mentioned statements of earlier writers,[1] and adds, as further proof, a peculiarity worthy of notice in many anæmic and chlorotic patients, viz. a considerable storing up of fat.

That a limited *increase in the metamorphosis of nitrogenous*

[1] See p. 190.

substances always took place in my experiments is shown in the following arrangement of their results. The excretion of urea here has relation to the unit of the loss of weight (see the following table, D).

It is clear that, notwithstanding a considerably increased discharge of water from the kidneys and increased excretion of urea, *the diminution of the body weight after blood-letting is not necessarily increased.*

TABLE D.

No. of Experiment	Hours of Fasting	Amount of Blood drawn per Cent. of Body Weight	Loss of Weight	Excretion of Urea	Urea per Kilo. of Weight lost	Condition of Urea before and after the Blood-letting
			Grms.	Grms.	Grms.	
I.	48–72	1·2	160	4·8	29·85	100
	72–96	—	126	6·1	48·33	162
II.	48–72	0·6	490	15·2	31·10	100
	72–96	—	440	13·8	31·43	101
III.	48–72	2·5	510	14·8	29·51	100
	72–96	—	444	22·4	50·47	171
IV.	48–72	1·3	550	8·1	14·79	100
	72–96	—	560	11·6	20·70	140
V.	48–72	2·7	130	2·1	15·77	100
	72–96	—	240	7·4	33·59	213
VII.	48–72	1·5	200	3·6	17·88	100
	72–96	—	200	5·5	27·61	154
IX.	48–72	3·4	137	2·5	18·25	100
	72–96	—	120	5·6	46·87	257
X.	48–72	2·7	305	6·2	20·17	100
	72–96	—	255	9·6	37·69	187
XI.	48–72	2·3	230	8·0	34·57	100
	72–96	—	254	11·9	46·87	136

Thus, to bring forward an example, in Experiment IX. after a depletion amounting to about 45 per cent. of the whole quantity of the blood, along with an increase of urine to double the former amount, the loss of weight per kilo. falls from 40·3 to 38·1 grms., and the urea increases more that twofold ($\frac{100}{243}$).

This, under the supposition of a consumption equally comprising all the components of tissue metamorphosis, would be inconceivable.

By calculation it can easily be proved that in my experi-

ments a regular diminution of the excretion through the skin and lungs in all probability took place, for if the calculation is not made under this supposition only absurd results are obtained.

I do not think that it would be interesting to expatiate more particularly on this subject. It would take up too much space to explain the conditions under which the calculation ought to be made.

Finally, by these calculations, only such numbers can be obtained as expressions for the facts as, to an unprejudiced and thinking mind, immediately result from the experimental data.

How is the action of blood-letting on the tissue metamorphosis to be explained?

We may assume, with Voit, that the albumen contained in the living body is not always and everywhere subject to the same conditions of decomposition. One part of it (*tissue albumen*) has become a solid constituent of the tissues; it changes proportionally slowly: another part (*circulating albumen*) is dissolved in the fluids, is driven with these through the body in the circulation, and is used up in the tissues without having first become an integral part of them. The quantity of albumen in the tissues depends on the quantity which circulates in the tissue fluids. A definite quantity of albumen in the tissues can only exist along with a corresponding quantity in the tissue fluids. If the quantity of circulating albumen is diminished, then part of the tissue albumen is set free from its more solid combination and becomes circulating albumen, and, indeed, just so much of it as is necessary to restore the equilibrium between the tissue albumen and the circulating albumen.

The same thing would occur if a saline solution of certain strength could take the place of the tissue fluids. Were we to dilute the blood by the introduction of water in place of a part of the tissue fluids contained in the vascular system, then the percentage of solids in the fluid contained in the tissues outside the vessels—which was at first higher—would, after the lapse of a certain time, become equal in amount to the smaller percentage within the vessels.

By a withdrawal of blood a diminution of the whole store

of circulating albumen contained in the fluids of the body is brought about. A corresponding part of the tissue albumen must therefore cease to exist as such and must become circulating albumen.

In a fasting condition the quantity of circulating albumen liable to be split up is an absolutely small one, and it is continually being renewed by the change of tissue albumen into circulating albumen. If this circulating albumen, in itself but a small quantity, is suddenly diminished in a considerable degree, then a proportionately large part of the tissue albumen must pass out of its combination in order to restore the equilibrium. The albumen thus set free is, however, subject to conditions of decomposition, and thus the high relative excretion of nitrogen in fasting dogs after blood-letting is easily understood.

The case is somewhat different in animals whose nitrogen remains constant. The absolute quantity of circulating albumen, maintained at an equal height by regular additions from without, is large in comparison with that found in fasting animals. The excess in the total amount of metabolism proceeding from the decomposed tissue albumen, which appears after bleeding, may be greater than in the fasting dog; but expressed as per cent. it will be less perceptible, as the other sum total—the amount of metabolism of the circulating albumen—is much more considerable. It is quite comprehensible, therefore, that the increase of the nitrogen in well-fed animals is absolutely greater than in fasting animals, but that it is smaller in comparison with the quantity of it that undergoes metabolism. Without further explanation, also, it is easily seen why in different individuals, notwithstanding an equal quantity of blood withdrawn, the increase in the elimination of nitrogen cannot have an equal value. This is the natural result of the varying quantity of nitrogen in the tissues, which finds its manifestation in the fact that for a given weight fasting animals excrete extremely different quantities of urea.[1]

That this explanation given by Bauer furnishes only a glance into the nature of the processes that follow blood-letting will

[1] See Tables A and B, pp. 221 and 223.

be doubted by no one; nor will it surprise anyone who is familiar with this difficult department of physiology—the department of tissue metamorphosis.

Objections have been raised by A. Fränkel [1] to the conclusions of Bauer on the basis of Voit's views, and an attempt is made to represent an entirely different factor, viz. the diminished supply of oxygen, as the cause of the increased decomposition of albumen. Fränkel supports his view by a statement of Traube's, which I give in its fundamental features.

'Every increase or diminution in the supply of albumen shows itself again in the excretion of nitrogen; when albumen is withheld from the food the excretion of nitrogen is reduced to its smallest quantity.'

Mechanical labour, which is accompanied by active transformation of non-nitrogenous substances and an abundant introduction of oxygen, increases the decomposition of albumen only in an extremely small degree. From this it may be concluded that 'the decomposition of the albumen is primarily a simple process of splitting up, which takes place independently of the oxidising action of oxygen; we further derive from this the important fact that the animal body possesses the power of decomposing not living, but only dead albuminous tissue matter; and that the quantity of the latter, whether it be introduced into the body from without or produced in it, alone acts definitely on the amount of the metabolism of the albumen.' Even the quantity of urea formed during the time when the food contains no albumen results from the death of living tissues taking place to a small extent. 'So far as the dead albumen of the food is not required for the renewal of the dead tissue—that is, for the formation of new organised tissue—it is at once decomposed, and the products springing from it are as quickly as possible removed from the body. Thus it is a peculiarity of the animal body to eliminate all dead nitrogenous substance found in it as if it were foreign to it, whilst living tissue is in no way affected by those agencies which bring about this decomposition and excretion.' Some

[1] *Virchow's Archiv*, vol. lxvii. 1876, and the discussion with Eichhorst in vols. lxx. lxxi. lxxiv.

pathological facts confirm the existence of this peculiarity in a singular way, especially the necrosis which is produced by cutting off the supply of blood, in which, when the process takes place in the midst of healthy tissue, a local process of decomposition must anatomically follow.

'The vitality not only of the whole animal organism, but also of all its organs and cellular constituents, is in the highest degree dependent on an *adequate supply of oxygen.* If this supply is sufficiently reduced the organs begin to die, and at the same time the increased excretion of nitrogen affords us a direct means of calculating the extent of this death.'

Fränkel, by artificially produced dyspnœa and inhalation of carbonic oxide gas, believed that he could bring about experimental conditions which would authorise him in ascribing to diminished absorption of oxygen the increased excretion of nitrogen observed by him after his very carefully performed experiments. There is no doubt that this idea has something very alluring in its perfect simplicity. Dead albumen is decomposed and thrown off; deficiency of oxygen causes death; loss of blood brings on deficiency of oxygen: and so the increased excretion of nitrogen after blood-letting is to be ascribed to the deficiency of oxygen thus produced. But, as things have hitherto been, the actual foundation appears to me to be wanting, for whenever one begins to reckon quantitatively—to take into account time and quantity—it is manifest that the case is not so. It would lead me too far were I here to give a detailed criticism of Fränkel's opinions. Certainly there remains a possibility that part of his suggestions may yet prove to be just and accurate.

The metabolism of *non-nitrogenous* substances after blood-letting assumes a more complicated form. After the lapse of about 24 hours there is manifest a distinct diminution in the excretion of carbonic acid. The explanation of this, as might be naturally inferred from Voit's views, would be that, with the diminution of the circulating albumen and the decrease necessarily accompanying it of the albumen firmly combined in the tissues, the conditions for decomposition in general have become less favourable. If a stronger expression is wanted, then it might be said, in the sense of this conception, that the

area in which decomposition takes place becomes smaller, since after bleeding a part of the organism has been destroyed.

To me a basis for definite ideas on this matter seems here to be wanting, for very few experiments are recorded bearing on this point.

The quantity of oxygen in the blood acts a subordinate part, as our chief concern is with the oxygen taken up by the tissues from the blood, not with that which is existent in the blood. It may be possible to demonstrate a diminution of the oxygen in the blood; if the tissues require more, then a sufficient quantity can be procured by increased activity of the heart and of the respiration; the mere deficiency in the blood is not sufficient to explain a diminution of what is consumed in the tissues.

Bauer observed that, in the *hours immediately succeeding* a *blood-letting*, the elimination of *carbonic acid* suffered *no diminution*, and this circumstance is explained by him in this way: 'Immediately after a withdrawal of blood, the cells of the various organs are still in their original good condition of nutrition; the materials in them are decomposed just as before, and on that account the same quantity of oxygen is taken into them.' This is a consequence which cannot be combated by him who adopts the fundamental views of Voit.

Bauer imagines that the breaking up of the molecule of albumen after venesection, takes place in much the same way as after phosphorus poisoning. The nitrogenous part of it falls under the conditions of thorough decomposition, and becomes completely oxidised into urea; the non-nitrogenous part remains behind in the cells themselves in the form of fat. Then comes on a true fatty degeneration. From a clinical point of view, this opinion has a great deal in its favour; the decisive facts will be mentioned in another connection.

Of special interest is the *increased elimination of water by the kidneys* after bleeding. This circumstance comes again most prominently into notice in the case of fasting dogs. It is certain that by blood-letting the whole quantity of water is diminished in no inconsiderable degree in the fasting body; we may regard the loss of water as amounting on an average to $\frac{4}{5}$ of the blood lost. Nevertheless, after blood has

been withdrawn, a very considerable increase in the elimination of water by the kidneys takes place; and indeed this rises in an almost equal proportion with the amount of blood withdrawn, and thus with the amount of water lost. A certain compensation, however, may take place from a diminution of the water eliminated by the lungs and skin. Probably this is not sufficient, as we may convince ourselves by calculation, and *there remains a fairly considerable increase in the elimination of water on the whole.* A convincing discussion of this physiologically highly interesting subject does not come within my range. I might only hint at two conditions which appear to me important.

The larger quantity of urea requires water for its elimination. In all probability there is a limit to the concentration of the urine, for in my experiments its specific gravity did not rise above 1,067 ; this corresponded to about 13 per cent of urea. If the products of retrograde metamorphosis accumulated in the body are to be got rid of, then the water required for the purpose must be supplied. The getting rid of them, however, is a condition, the non-fulfilment of which endangers the existence of the whole organism.[1] Thus, then, a larger quantity of water is lost, at least for the time; afterwards, however, by restricting the elimination at other points, the equilibrium may be restored.

The tissue fluids contain less albumen and more water than the blood. If these become mixed with the residue left in the vessels after the withdrawal of blood, then the relative quantities of water and solid substances, such as albumen, in the blood become altered. The question arises whether a compensatory excretion of water might not be of use in order to procure the most favourable conditions for the nutrition of the tissues; or, to express it differently, whether the blood, as an organ, is not striving to maintain its function in a condition as nearly as possible approaching the normal one. Both points have hitherto been so little discussed in a scientific manner that at the most they can only be noticed by way of suggestion.

[1] See Voit, *Zeitschrift für Biologie*, vol. iv. p. 154 et seq.

Here the subject of the *heat of the body* after blood-letting may find suitable mention. Precise observations with regard to human beings are not to be had; there exist only incidental experiences. Wunderlich states that in health the effect of a moderate withdrawal of blood is small. After free venesection, the temperature rises to the extent of a few tenths of a degree; in the days immediately following, it returns gradually to the normal state, and afterwards may even sink beneath it. This is the result of Bärensprung's observations. If, with reference to the subject that is now to come under consideration, patients suffering from gastric ulcer, or women who, until accidental abortion occurred, were in a perfectly normal condition, may be regarded as healthy persons, then we have occasionally opportunity to observe the influence of severe losses of blood. The first striking circumstance is that great individual differences exist. Many people endure severe bleeding without any considerable diminution of their bodily heat; usually, however, the temperature falls quickly and considerably: in the rectum it may be as low as 34° C. (93·2° F.), even though every effort has been made from the beginning to prevent as far as possible the loss of heat.

How far an increase of temperature succeeding loss of blood may possibly be occasioned by such a loss, is a question which must be left undecided. It is even, after particular consideration of all the circumstances in individual cases, very difficult to attain to a definite judgment. Experiments on animals can only be accepted with great reservations. The regularity in the course of bodily heat which is to be found in an adult human being is wanting in animals so far as can be generally inferred from the very imperfect observations that have been made; particular investigations on this subject are even wanting on the species of animals which are most frequently used for physiological purposes.

Marshall Hall, in his experiments in the year 1830, has investigated the effect of the loss of blood on bodily heat.

His observations on dogs extended over several consecutive days; the blood-letting was performed gradually, at intervals.

Thus in Experiment II., begun on November 6, there were withdrawn from a dog of 16 lbs. weight—

Nov. 6	11·0 oz. of blood.		Nov. 16	2·75 oz. of blood.
„ 8	5·5 „		„ 17	3·75 „
„ 11	3·25 „		„ 18	2·50 „
„ 13	4·75 „		„ 19	2·25 „
„ 14	4·0 „		„ 20	6·75 „
„ 15	4·25 „		„ 22	6·50 „

Thus, on the whole, 56·75 ounces were drawn in the course of 17 days. The temperature, measured under the tongue and in the back part of the mouth, varied between 101° F. (38·4° C.), on the 1st and 3rd days after the beginning of the operation, and 96° F. (35·6° C.), which was for the most part observed during the last three days of the experiment.

Experiments by Spielmann, Frese, and Choraszewski [1] proved that in dogs and rabits, immediately after a venesection, the thermometer falls to the extent of about 1° C. (1·8° F.), (from 0·3° C. to 1·8° C. are the limits); afterwards it rises again and ascends above the normal height (0·7° C. to 1·8° C.) (1·3° F. to 3·2° F.)

A discussion of the febrile condition in man is not admissible here. What happens then will be afterwards discussed.[2]

We know something of *the change in the activity of the large glands connected with digestion.*

Manassein [3] found that after losses of blood the *gastric juice* of dogs does not digest albumen so thoroughly. It turned out that deficiency of acid was the cause of this.

Ranke [4] found that in guinea pigs, after a loss of blood, the *bile secretion* decreases—indeed, entirely ceases—with an amount of blood lost which admits of unenfeebled cardiac, muscular, and nervous activity.

A knowledge of the influence which loss of blood exerts on the *central organs of the nervous system* is of primary importance.

Marshall Hall, to whom, as we know, we are indebted for insight into that hydrocephaloid disease of children which depends on cerebral anæmia, has already thoroughly gone into

[1] See Landois, *Die Transfusion des Blutes*, p. 147. Leipzig, Vogel, 1875.

[2] See below, p. 241 et seq.

[3] *Virchow's Archiv*, vol. lv. 1872, p. 413 et seq.

[4] *Die Blutvertheilung und der Thätigkeitswechsel der Organe*, pp. 116 and 190 et seq. Leipzig, Engelmann, 1871.

this question. The general symptoms have been already discussed.[1] Fainting, coma, convulsions, delirium, were formerly frequently observed when a depletion was carried on too long and to too great an extent. Although the facts obtained from clinical observation can hardly admit of a doubt as to the causal connection between loss of blood and impairment of the activity of the skin, yet Marshall Hall has made experiments on animals for the purpose of enlarging and completing these clinical observations. Thorough explanations have been obtained by the investigations of Kussmaul and Tenner.[2] The principal results of these are—

The convulsions, very much resembling an epileptic type, which are often seen in bleeding animals, are caused by a *sudden* interruption of the *arterial* supply of blood to the brain.

The sudden interruption of the nutrition of the brain, not an alteration of pressure, has most to do with these convulsions.

Convulsions do not occur in bleeding, when the operation goes on slowly, or when the animals are very weak.

The *central origin of the convulsions* is to be sought in the excitable regions of the brain, which are situated behind the optic lobes.

Unconsciousness, *loss of sensation*, *paralysis*, are produced in man by interruption of the supply of arterial blood to the parts lying in front of the crura cerebri.

Certain centres of the brain and of the medulla oblongata are also, as it appears, affected by the loss of blood.

Here we must refer to the adaptation of the vascular system to the changing quantity of its contents, which was formerly discussed. So also in the description given by Marshall Hall of 'excessive reaction' the symptoms in connection with the circulation must really be ascribed to the influence of the nervous system and not ultimately to the vasomotor system.

The *respiratory centre* is also affected.

It has actually been found by Leichtenstern[3] that *immediately* after blood-letting the extent of the respiration, i.e.

[1] See above, p. 188 et seq.

[2] *Untersuchungen über Ursprung und Wesen der fallsuchtartigen Zuckungen bei der Verblutung*. Frankfort o. M., Meidinger, 1857.

[3] *Zeitschrift für Biologie*, vol. vii. p. 215 et seq.

the quantity of air breathed or renewed in a given time, diminishes.[1] This, however, does not long continue, and the respiration soon reaches its former extent again. It is only by very considerable withdrawals of blood that the extent of the respiration is permanently diminished—such as in Leichtenstern's experiment on a large rabbit, in which, in the course of about 5 hours, 10 c.cm. of blood were withdrawn at four separate times, then 5 c.cm., and finally 10 c.cm.

The *number* and *depth* of the respirations are similarly affected. They fluctuate constantly to a certain extent; only immediately after a withdrawal of blood a temporary decrease in the number and depth takes place.

If the blood withdrawn has been very abundant, then the frequency of the breathing ultimately increases.

Certain peculiarities of the *respiratory rhythm*, especially the Cheyne Stokes phenomenon, are not unfrequently seen, more or less distinctly marked, after loss of blood. Exhaustion of muscle and nerve may have its share in these phenomena, but they are concerned essentially with the changes in the excitability of the nerve centres.

Impairment of vision amounting to entire blindness in one or indeed both eyes occurs after loss of blood, often while the blood is still flowing, at other times not until long after. Whether here central or peripheral changes are present appears not yet decided; perhaps both may be assumed to take place, varying in the individual case. It is of practical importance to be aware of the fact that in the majority of such cases the impairment or even the entire loss of sight is permanent.[2]

Whatever may be the action of blood-letting on the *muscular system*, a lessening of its capability of work is certain. It will depend on the extent of the loss of blood and on the demand made on the individual muscle, or on the whole muscular system, whether outwardly this diminished capacity of work is seen and felt, or not. In general, it may be said that the greater the activity of the individual muscle, so much the more readily will

[1] Such an one of five minutes' duration was selected.

[2] See the careful work of Fries, *Beitrag zur Kenntniss der Amblyopieen und Amaurosen nach Blutverlust*, Dissertation, Tübingen, 1875; as also the Supplement of the *Klinische Monatsblätter für Augenheilkunde*, edited by Zehender.

the diminution of its active power, produced by the venesection, become evident.

The supposition is ventured with hesitation, that, with more severe demands, an originally functional capacity may end in an anatomical incapacity, as the nourishment cannot keep equal pace with the increased waste.

In order to form a judgment of the *therapeutic value* which blood-letting may have, there are various experimentally well-established facts which may be regarded as decisive.

It must never be forgotten that, even when the quantity of blood is very considerably diminished, the *decrease of pressure within the arteries is only of short duration.* So also it is a highly important fact that the *loss resulting from a depletion is not limited to the blood itself, but that a larger or smaller part of the tissues of the body is lost along with it. Fatty degeneration* often attacks the organs that are most necessary to life and its undisturbed continuance : for it is also worthy of remark that *up to the moment when the red blood-corpuscles, which have been removed by the blood-letting, are replaced, the quantity of hæmoglobin in a given quantity of blood, and therefore the oxygen-combining surface in it, is smaller.* If the body requires, from any cause whatever, more oxygen, then a more frequent return of the blood current to the place where oxygen is absorbed, viz. the lungs, is necessary. This requires an *increase of the propulsive power* of the heart and of the respiratory muscles. It must be remembered that the *demand for an increased nutrition* of the work-producing muscles goes along with an increased performance of work. The fact that, after losses of blood, it is the *heart* itself which most frequently manifests functional impairments—not seldom fatty degeneration—goes far to support the conjecture that a disproportion between renewal and waste may often manifest itself exactly in this organ. If the power of the heart, however, decreases, then the nutrition and the capacity for action and resistance of all the other organs decreases also ; for these organs are now supplied with not only less valuable blood, but also in an insufficient degree. Daily experience affords ample proof in justification of this view. An anæmic patient comes to the full consciousness of his small capacity for exertion from the

moment when the claims on him exceed the minimum. In a slow walk on the level he can keep pace with the others; but if the pace is accelerated, or if it is necessary to ascend a moderate height, then the panting respiration and quick pulse betray the deficiency of oxygen, and the frequent halting shows the incapacity of quickly supplying that deficiency.

The injury done to the whole organism clearly proceeds from a cause, of the existence of which we may often enough assure ourselves; œdema shows itself in those parts of the body which, by virtue of gravity acting to hinder and delay the blood stream, are best fitted to exhibit the effect of a blood supply which is abnormally constituted and is not made to circulate with sufficient rapidity. That is to say, instead of vessels which, under normal conditions, spontaneously regulate the exchange between the blood and the tissue fluid, we have mere tubes, permitting of filtration through them in obedience to simple pressure. What ought to be taken up into the blood remains behind in the tissues, and alters the tissue metamorphosis, at least makes it so slow that on the whole a diminished activity is brought about. We need only to remember the axioms: The circulation of the blood is necessary in order that life may continue, since by its means oxygen is carried to every organ. The functional activity of every single part is dependent on the presence of a certain quantity of oxygen, increasing with increase of function. From a consideration of these we must conclude *that no loss of blood in itself can be profitable.*

Of course, along with this, we must also acknowledge that even a considerable depletion brings no essential injury to thoroughly strong, healthy individuals. But we must never forget that, in by far the greater number of cases (there are, it is true, exceptions), in which we resort to the withdrawal of blood for therapeutic purposes, we have to do with an organism which has already been injured by disease.

Whoever looks upon depletion as a sacrifice ought to ask himself whether there are not circumstances in which this sacrifice is necessary for the good of the whole. Perhaps we may be able to lay down rules, the observance of which, although in general advisable, ought perhaps to be left as a matter to be decided by the conditions of the individual case. It is here

that the *experience of the physician* becomes of the greatest importance.

In every disease which is at present classified under the heading of infectious diseases—the plague, typhoid conditions, acute exanthematic fevers, diphtheria, malaria, &c.—the opinion, that the employment of blood-letting, and of nothing else, is wrong, is confirmed by the observations of centuries. The more rarely in great epidemics blood-letting was practised so much the greater was the probability of recovery: so we are taught by the united testimony of temperate and unprejudiced physicians. If there be anyone to whom this statement appears too dogmatic, he will find collected together in the works of Haeser and Hirsch the facts on which it is founded.

Disregarding Broussais, who simply selected 'inflammation' as the point to be attacked by his treatment, we may regard, as the basis of the treatment by blood-letting in infectious diseases, the idea that a portion of the virus contained in the blood, and which sets up the disease, is thus got rid of. This involves the further supposition that the mischief is contained in the blood itself; also that, with a diminution of the quantity of the blood, a later but not entire restoration of the mischief takes place, which may ensue more slowly than the complete renewal of the blood. Or we must consider that a decrease of the exciting cause of the disease, though only a temporary one, is of more importance than the loss of blood which is combined with it.

The formula stands thus:—

The something that causes the disease is in the blood.

The severity of the disease depends on the quantity of this something; the greater the quantity, the more severe the illness, and the greater the danger to life. By means of blood-letting we decrease the quantity of the active cause of the disease, also the severity of the latter, and with this the danger to life.

If the premises were as simple as the conclusions then there would not be much to bring against this view of the matter; but a little deeper criticism teaches us that they are not so simple.

Does, therefore, the development and maturation of the

active cause of the disease really take place in the blood, and is the latter the place in which it breeds?

Or is the poison, having been produced somewhere else, merely distributed over the whole body by means of the blood?

In many diseases we know with certainty, in the majority we conjecture, supported on good grounds, that local infection produces local foci of disease; the disease spreads by the extension of these, and by new deposits, and finally there is the wider spread of the mischief, in which the blood plays the part of a medium of circulation, if it is at all concerned in the matter.

A primary disease of the blood caused by infection has not been observed with certainty.

If this be correct, then we need no further details as to the unstable ground on which the whole structure stands. Even if a part of the morbific virus be removed with the blood it will be quickly replaced from the germinal foci existing within the body. The blood does not recover from its loss so quickly; it is poorer in hæmoglobin and in oxygen. The fever which is never absent under such circumstances is more exacting; the body needs more oxygen, so that the heart must still further increase its already augmented activity. Thus the possibility of its failure is approached.

Therefore, even when looked at from the theoretical standpoint, depletion is forbidden as a remedy in infectious diseases.

What, however, is to be reckoned as an infectious disease?

It would be presumptuous to draw the line just now, when sure indications could scarcely be found, owing to the growing belief in the doctrine of the infection of the body by means of organised substances. It appears to me that more thorough observation of the etiological conditions, such as every physician can make at the bedside, brings to the investigator real support for his views. I therefore consider that a great crowd of allied diseases which until now have remained outside the barrier, will soon follow croupous pneumonia and acute articular rheumatism. But this is only an opinion.

We shall arrive at a judgment of this matter best by weighing the possible usefulness of a withdrawal of blood, in the doubtful diseases which, according to custom, are included with

the 'inflammatory' ones, against the injury which always accompanies a loss of blood. The adherents of the practice of venesection give us certain opinions as to the usefulness of it, the true value of which, however, has yet to be tested. On the other hand a circumstance which is very weighty must be brought forward.

Withdrawal of blood increases the decomposition of albumen just as fever does. The diseases which are to be considered in this connection are accompanied with fever. In a febrile disease there takes place, therefore, when venesection is practised, a double attack on the albumen in the body; and a diminution of its quantity to a considerable extent ensues. We must always carefully consider whether the body of the patient is in a position to bear this; whether the practice of venesection is so very advantageous that the disadvantage which undoubtedly ensues is outweighed by it. Here we must remember that fever and depletion, by lowering the activity of the glandular apparatus which is absolutely necessary for the absorption of restorative material from the food, render this absorption more difficult. A withdrawal of blood, therefore, from a patient with fever has much greater effect than when it is practised on one who is free from fever.

Let us now consider what useful results were expected and what, in practice, have been actually obtained.

Venesection is said to be in a position to limit the 'inflammation,' and when used at the right time to be able to cut short very often, if not always, the development of the disease —at any rate to arrest it as a whole. This is an aim which, if attainable, is worth the sacrifice. Without being indiscreet we may indeed ask the question, Why? Is it because fewer people die? A proof of this, which, if it could be obtained, would be quite sufficient, is wanting, and, judging from the communications which have been made up to the present, is scarcely to be sought with any prospect of success.

Is it because Hippocrates, Galen, and others up to the time of Traube have taught it?

I fear that a physician, who is absolutely convinced that facts, and not names, be they never so eminent, must decide, will scarcely be content with such proof.

Still we must give to certain facts their full value.

At least one point that can be grasped stands out from the whole subject of the antiphlogistic action of venesection. We have firm ground under us in forming a judgment on the *antipyretic influence of a blood withdrawal.* For it must be looked upon as certain that there can be no talk of decrease of fever so long as the thermometer shows a very great difference in the temperature—a considerable increase above the normal.

He is mistaken who believes that the statement, that venesection decreases fever, is supported by accurate determinations of temperature. One fact, indeed, is indisputable: the hæmorrhages which sometimes take place in enteric fever, whenever they are at all considerable, decrease the heat of the body for at least half a day. It is a question, however, whether this observation can be generalised and applied to feverish conditions as a whole. By far the greatest number of intestinal hæmorrhages take place at a time when the fever has already passed its highest point; the temperature, after all treatment which aims at lowering it, sinks to a lower point, and then again more slowly rises. The action of venesection will therefore under these circumstances be felt more strongly. This undoubtedly is readily noticed as soon as affections which are at their full height and accompanied by continuous fever are taken into consideration.

Traube [1] has taught with perfect right that *the temperature-decreasing effect of depletion is one which quickly passes off*, as far as he observed it in cases which were just at their acme. He, however, gives us only scanty casuistic material, but as far as I know it has not been contradicted.

Traube's first case may serve as proof.

A strongly built, well-fed butcher, of twenty-six years of age, was brought into hospital suffering from a left-sided pleuropneumonia of four days' standing. The temperature was—From 5 to 6 o'clock in the evening of the fourth day of the disease, 41·1° C. (106° F.); from 10 to 11 in the morning of the fifth day of the disease, 40·9° C. (105·6° F.) About six minutes past 11 blood was taken to the extent of 14 oz.; the

[1] *Gesammelte Abhandlungen*, vol. ii. p. 227.

blood flowed out in a thick stream; *the temperature of the body an hour after venesection was unchanged.* From 5 to 6 in the evening of the fifth day of the disease, 40·2° C. (104·5° F.); about 10 o'clock in the morning of the sixth day of the disease, 39·5° C. (103·1° F.); 'in the evening' (no more precise statement) of the sixth day of the disease, 41·0° C. (105·8° F.), though about 37 minutes past 4, but before the measurement of the temperature, 8 oz. more blood were withdrawn; 10 to 11 o'clock in the morning of the seventh day, 39·40° C., after an outbreak of copious perspiration had taken place a short time previously. Then a quick fall of the temperature and disappearance of every symptom of the disease.

If it is granted that every fall in bodily heat is to be ascribed to the venesection, though even this is not unquestionable, it is, at all events, certain that *a very considerable withdrawal of blood, according to therapeutical reckoning, can neither in a short time nor to a great extent succeed in lessening a febrile condition while still at its height.*

A second case reported by Traube is less simple. A convalescent from typhoid fever was seized with pneumonia. As his system had been enfeebled by previous illness, cupping was practised, and blood was withdrawn to the extent of 6 oz., which in Traube's opinion acted energetically on the temperature. Even if this opinion is accepted without contradiction, nothing would be gained in favour of the therapeutical application of venesection at the commencement of acute febrile conditions; for one would not readily wish to draw the inference that only in weak individuals is a withdrawal of blood imperative as an antipyretic remedy. It is only necessary to attend to the teaching of experience received at the bedside of a typhoid patient, in order to feel an inward doubt arise as to whether in reality blood-letting is so harmless in 'inflammatory' diseases, as pleurisy and pericarditis; and this doubt will arise in spite of all aversion we may feel to the opinions founded on physiological grounds, and in spite of all the reverence with which we may regard the therapeutical statements of our great ancestors. A greater mortality and a convalescence of longer duration are seen among typhoid patients after spontaneous losses of blood. But pleurisy and pericarditis meet here to-

gether with typhoid, inasmuch as in these three, in contradistinction to that kind of pneumonia which has a typical course and a comparatively short duration, we have to do with conditions which are from an early period combined with fever of long duration and with great wasting. The warning which was uttered long ago by excellent observers—I name only Wintrich, Ziemssen, Niemeyer, Wunderlich—that, in treating pleurisy, one must reckon on a long duration, and therefore must abstain from weakening measures, appears so well warranted that the unsupported assertions of others against it have little weight. Surely a little consideration will prevent blood-letting being performed for the sake of less than ephemeral success, which may be better—and with less risk—obtained by other means, and especially since for the patient depletion implies a severe or indeed irreparable loss. I am of opinion that it must have happened to good observers in times past just as to those of our own time, who, spending their years of apprenticeship in the traditions of antiphlogosis, have in their more mature age come to see that blood-letting was not needed. Why, then, in this matter must the authority be accepted as valid of those whose lips death had closed before they could say, 'We were in error'?

It is not so easy to pass judgment on the assertion, that *in inflammatory diseases a venesection practised at the right time may hinder or absolutely suppress the development of the disease.* An objective measure is wanting, such as the thermometer supplies in the fever question. The very circumstance that the diseases under consideration are such as do not run a typical course, and that the duration and severity of each individual case cannot be predetermined, must admonish us to be cautious. As sufficient statistics, which would require to be very considerable, are wanting, and as it is easy to foresee that a theoretic discussion, added to our present theory of inflammation, would give an entirely negative decision, we can make only a very general statement here. That good and careful observers have seen pleurisy, &c., quickly disappear after venesection, is not at all to be disputed; and that they, having first laid it down as a settled point that blood-letting is indispensable in 'combating' these diseases, inferred that venesection, practised at the right time, will quickly check the disease, is only a

logical sequence. But, whenever it can be proved that without venesection a favourable termination may also follow, that without venesection even rapid absorption of an exudation, which physically was demonstrable in considerable quantity, is possible, there is no need to call in question the accuracy of the observation in order to prove that the inference drawn from it is incorrect. The reference to the authority of the 'grave' also loses its value here. He who was not in a position to see may have possessed the best eyes, but yet he could not observe what was withdrawn from his view. The fact of the spontaneous disappearance of such inflammations was, however, not formerly known; and the probability that a causal connection exists between the blood-letting and the checking of the disease appears not to be specially supported by the statement of the above-mentioned good observers, viz. that *only exceptionally a cutting short of the whole process or a questionable hindering of its development takes place.*

Anyone who may express his opinion without prejudice must be permitted to say, with all reverence to the great past, that one of those errors may here exist from which no mortal escapes, as he always remains a son of the times in which he lives.

The *present state of the case* may be thus stated: it is neither proved, nor even shown to be probable, that the development of acute inflammatory diseases is hindered or prevented by blood-letting; and considering the undoubted injury which every loss of blood causes, especially when conditions of weakness exist or are on the point of being developed, *it is not advisable to practise blood-letting in such cases.*

It is a fact, not unworthy of consideration, that the inflammations formerly arranged in one group have gradually resolved themselves in a therapeutic sense into subdivisions which, although rather forcing themselves on the general feeling, than supported by any good grounds, yet somewhat correspond to what they might be if etiologically arranged. The anatomical changes are the same in inflammation wherever it takes place, and yet an advocate of the full antiphlogistic method in pleurisy would hardly be inclined to follow the prescriptions which were formerly given for the treatment of local inflammation in general.

We read, for instance, in Richter,[1] who may be designated a wise eclectic (I quote from his 'Etiology' the treatment of *gastritis toxica* as a subject suitable to the present state of the discussion), that in gastric inflammation, 'as being a really acute inflammation, the antiphlogistic treatment in its widest application is necessary, and therefore before everything else depletions must be boldly practised on account of the pressing danger.' 'But,' it is added, 'the indications here are *not* violent inflammatory fever, and a full and hard pulse—these never accompany gastric inflammation. On the contrary, the smaller and feebler the pulse and the colder the extremities are, the weaker even to fainting the patient feels, and the greater the nervous disturbance is (all this, of course, being combined with distinct symptoms of gastric inflammation), so much the more boldly can and must blood be drawn. At first general venesections are to be performed, and their amount will depend on well-known conditions. From these there is nothing to fear, not even if syncope ensue. They are to be repeated whenever the attacks are renewed, and especially when the pulse again becomes very small and hard. After general depletion, but not before, local blood-letting over the region of the stomach is suitable.'

The same method is pursued in treating inflammation of the liver, spleen, &c.

If at the present day voices are raised in favour of local blood-letting in local inflammations, it is hardly likely that anyone will advocate general blood-letting whenever the question turns upon processes which are undoubtedly limited and produced by simple causes of inflammation.

In other respects the whole development of pathology consists in this: to follow out more closely what are at present comprehended only in their outward aspects, the primary causes which lie at the foundation of the anatomical changes and the symptoms of diseased processes. That it is impossible to get out of the difficulty by that help in all need, the ambiguous term 'a cold,' will be evident to any physician who has preserved his senses and his common sense in the simple processes of everyday life. Why, then, under similar outward conditions—at

[1] *Die specielle Therapie*, vol. i. p. 563. Berlin, Nicolai, 1812.

least we find no difference—is there at one time increased pain, at another time bronchial catarrh, and the third time a general feeling of well-being? As soon as specific morbid causes for these 'colds' can also be shown, even he who is most prejudiced in favour of blood-letting must abstain from this practice more than has yet been done.

Among the general indications for blood-letting there still remains that condition formerly known by the name of 'plethora.' A thorough statement of the case founded on experiment will have a place in another connection. Here it may be mentioned that the question turns upon something, the existence of which is not proved, and in fact can scarcely be proved. We must, from the standpoint of our present knowledge, express the opinion that plethora, as a permanent anomaly of the constitution, does not, and cannot, exist. With this decision all further discussion of the benefits of venesection in these circumstances falls to the ground as irrelevant.[1]

We come now to another side of the question as to the therapeutical value of blood-letting.

That a place in the *indicatio causalis* or the *indicatio morbi* (to use the traditional scholastic expressions) cannot be assigned to blood-letting clearly appears indisputable. Perhaps among the numerous folds of the mantle of *indicatio symptomatica* it may find a resting-place with a provision for old age; there is no want of goodwill to give it such a place. We recognise in our present medical textbooks the earnest effort to prevent blood-letting from falling entirely into disuse, even though the author in his own practice seldom or never employs it. The tradition of so many centuries continues to affect us; it loses from decade to decade something of its influence, but there is an unwillingness to lay it aside altogether.

As the special therapeutics are now to be considered, and as the circulation in the organs which are here to be mentioned is somewhat peculiarly arranged, separate consideration of each organ is necessary.

Let us begin with the *brain*.

The following summary fairly represents the amount of our

[1] We may compare amongst earlier writers Wunderlich's temperate description, *Handbuch*, i. p. 355 and iv. p. 544 et seq.

present knowledge with regard to the circulation in this organ:—The contents of the cranium, enclosed in a firm capsule, are unchangeable so far as their volume is concerned; a compression of these contents, by means of the normally available powers of pressure of the body, cannot take place.

On the other hand the contents of the cranial cavity may be variously constituted; the blood and cerebro-spinal fluid may exist in different proportions; the more blood, so much the less cerebro-spinal fluid, and *vice versa*. The possibility of this alteration is caused by the widespread connection which exists between the cerebro-spinal fluid and the lymph vessels, by means of which connection the flow of the fluid into these vessels, and combined with this its absorption into the general circulation, is secured. Moreover the ligaments of the vertebral column may be stretched by the pressure of the cerebro-spinal fluid, and thus a space capable of extension to a certain degree is created for the relief of the highly-pressed fluid in the cranial cavity.

The amount of blood in the brain is dependent on the activity of the heart and the vessels. The normal pressure acting on the contents of the cranium is not the whole of the pressure within the intracranial arterial system. It is that pressure diminished by the resistance of the elastic walls of the vessels and by their muscular action.

It is accepted as probable that *a simple increase of the arterial pressure, produced by increased activity of the heart, is quite capable of producing an increase of pressure within the cranium sufficiently great to hinder the flow of blood in the capillaries of the brain; to hinder it to such a degree as that impairment of the activity of the brain may be the result.*

The reasoning is nearly as follows:—[1]

1. Increased activity of the left ventricle causes increased fulness of the cerebral arteries. By this means the cerebro-spinal fluid contained in the perivascular spaces of these vessels is forced into the space beneath the pia mater, and at last into that of the spinal cord. Thus the whole cerebro-spinal fluid is submitted to high pressure.

[1] We may compare Huguenin, *Ziemssen's Handbuch*, vol. xi. i. 2nd edit. p. 437 et seq. and p. 846 et seq.

2. By increased activity of the left ventricle the pressure of the blood on the inner wall of the arteries of the brain may become so considerable that it may be able entirely, or at least for the most part, to overcome the elastic tension of the wall of the arteries along with the resistance made by the non-striped muscles. The brain and cerebro-spinal fluid are then both submitted to a pressure nearly equal to that prevailing in the arteries.

3. The consequence of this increase of tension, affecting the whole contents of the cranium, is a more or less considerable compression of the capillary vessels in the brain and spinal cord, which causes a hindrance to, and therefore a slowing of, the flow of blood in the capillary region; and from this proceeds an impairment of function.

However lucid the thing appears, still, in my opinion, on closer examination there arise difficulties and doubts which I cannot succeed in setting aside.

Firstly:

It may be admitted that increased activity of the heart really produces increased fulness of the cerebral arteries and displacement of the cerebro-spinal fluid contained in the perivascular spaces. It would not, however, be then proved that by this means even a transiently, not to speak of a permanently, increased pressure of the cerebro-spinal fluid on the whole would necessarily take place. *This would presuppose that an accelerated flow of lymph under these conditions did not take place;* but Bergmann has shown *that in fact during fluxional hyperæmia the lymph flows more rapidly away.* That permanently increased pressure of the cerebro-spinal fluid is produced by increase of fulness of the cerebral arteries and greater pressure of the blood contained in them, is certainly not hereby proved, and indeed is improbable.

Secondly:

The increased activity of the heart is said to be sufficient entirely or nearly to overcome the elasticity and the muscular tonus in the cerebral arteries. This supposition must be difficult to prove; it contradicts the facts known about the circulation, and has, indeed, no experimental basis.

Increased activity of the heart tends to increase the differ-

ence in pressure between the arteries and the veins, and thus to accelerate the circulation of the blood. Why, then, should this axiom, which is generally true, not be also true with regard to the brain? If the tonus were removed from the arteries, and if an over-straining of their elasticity had supervened, then the matter would be worthy of consideration. But is the vital energy supplied by even a powerfully-acting hypertrophied left ventricle sufficient for such a mechanical achievement? And if that question could be answered in the affirmative, why does such a thing happen especially in the brain? why not also in the spleen, the stomach, or the intestines? What we see at the bedside does not exactly speak in favour of the accuracy of this view. How often all goes on well in spite of the most turbulent action of a hypertrophied left ventricle, even with strongly atheromatous arteries! how quickly after symptoms, which are usually ascribed to the causes here spoken of, does the clinical condition return to the normal! According to all experience with regard to over-straining, it can scarcely be supposed that the cerebral arteries should form an exception to the general rule, and after a short space recover their former elasticity.

Thirdly:

That increased pressure of the cerebro-spinal fluid may cause a compression of the capillaries of the brain cannot be disputed. But it is not proved that actual fluxional hyperæmia conduces to such an increase of pressure; on the contrary, the improbability of such an occurrence is evident.

But this is not enough. After unprejudiced consideration of the whole matter the question comes to be asked, *Whether indeed arterial fluxion is generally associated with symptoms of impaired activity of the brain?*

Special symptoms which would belong exclusively to such arterial fluxions are not known. Giddiness, headache, forgetfulness, excessive irritability of the mind and of the nerves of sense, inability for work, sleeplessness; frequently flushing of the face, the feeling of passing heat, painful throbbing of the arteries in the neck and head—from signs so various in their significance, appearing with every possible functional disturbance of the brain, we can never lay the foundation of an

anatomical diagnosis. What is there that has not been called cerebral hyperæmia? Nothnagel[1] distinguishes many things from it; the mental changes that take place in old age, and states of febrile exaltation, he does not reckon among this class of diseases. He plainly says that cerebral hyperæmia and anæmia resemble each other clinically, so as to be mistaken for each other—indeed, are actually entirely alike. But in my opinion even he does not go far enough. Nothnagel claims for certain mental disturbances an affinity with fluxional cerebral hyperæmia; excitement amounting to mania, which shows itself in paroxysms with lucid intervals, and even distinct mental delusions which occupy the patient during his attacks, this investigator will not banish from the domain of fluxional hyperæmia of the brain, notwithstanding all his reserve in passing an opinion.

It appears to me that we have much to put to rights in the heritage left us from that period in which anatomical diagnosis so occupied the mind that it was considered necessary to assign an anatomical place to every diseased disturbance of function of an organ, even were it in the nomadic tent of hyperæmia or anæmia. It was also then easy to hold fast the scholastic doctrine, when post-mortem examination proved nothing; the statement is, and was, accepted, against which there is little to be said, that arterial hyperæmia is not by any means always demonstrable post mortem. From all that I have myself seen and read of the conditions of so called active hyperæmia of the brain, I am of opinion that it is to be considered as a very artificial mosaic picture, the single stones of which have been brought together from very remote regions. Every argument, which would refer hindered circulation in a purely mechanical way to increased arterial blood-supply, does not appear to me convincing. As primary causes of the series of symptoms on which the title of cerebral hyperæmia has been conferred I might mention several.

'Apoplectic cerebral congestion' I hold with Nothnagel, following Trousseau's precedent, to be of decidedly epileptic origin; and a considerable number of less important forms of hyperæmia appear to me to belong also to the epileptic group.

[1] *Ziemssen's Handbuch*, vol. xi. i. 2nd edit. p. 34 et seq.

Others are the results of chronic poisoning, especially by tobacco and alcohol.

A considerable number of the so called cerebral hyperæmiæ are of an inflammatory nature. They accompany the changes in the vessels which are peculiar to inflammation. The region here to be trodden is indeed a very dark one; but the fact, that a cause of disease is active here, varying in its strength, but identical in its nature, is suggested by the appearance of such 'cerebral hyperæmiæ' in groups, and that in these groups almost always one or another case runs clinically and anatomically the course of a genuine meningitis—a fact of which we have only too much opportunity of convincing ourselves.

Much still remains, which is somewhat inaccessible to more precise knowledge.

It admits certainly of no doubt that the vessels of the brain can be reflexly acted on. But in the usual description of 'relaxed or passive hyperæmia' there is, as it appears to me, much which must not be accepted as a simple statement of the truth. It is maintained that, often without any direct injury from without, an entire cessation of arterial tonus in the brain may take place, and then the elastic resistance of the wall is completely overcome by the pressure of the blood, which is not necessarily increased above the normal amount, and the pressure of the intracranial arterial system is thus transferred undiminished to the brain. The consideration formerly brought forward I would here repeat and once more enforce, that in an organ, as the brain, which has at command so many channels of escape by means of veins and lymph vessels, it would be somewhat difficult for the medium pressure to be exceeded. I suggest still further in support of this opinion that, when the outflow of venous blood from the cranium is hindered to a considerable extent, symptoms of cerebral pressure are more frequently absent than present, even though, apart from all collateral circumstances, the penetrability of the vessel wall, increased by venous stasis and thus favouring the production of these symptoms, is associated with it. Notwithstanding all this, we do not find in the majority of cases, even when undoubted moderate insufficiency of the tricuspid exists, that signs of hyperæmia of the brain are met with at the post-mortem

examination, though we may observe that an increased quantity of venous blood is undoubtedly present. Let it not be objected that in such cases we have to do with conditions that have been slowly produced, and to which the organ has therefore become accustomed. An acute bronchial catarrh may very suddenly bring a person suffering from emphysema or cardiac weakness, who has hitherto been tolerably capable of work, to the verge of death; cerebral hyperæmia does not require to give tokens of its existence. The very fulness of the returning canals is a protection against it, and the system of the lymphatics and veins is capable of affording assistance.

We may twist and turn the matter as we please; we must always come back to this point, that simple mechanical hindrance to the capillary circulation in the brain does not take place by an increased fulness of its arteries, nor, we may probably add, of its veins; at all events, it does not produce the symptoms which are usually attributed to it.

It is quite otherwise *whenever causes which excite inflammation act on the vessels of the brain.* Then, indeed, all that may happen which has been ascribed to increased arterial flow. The increased pressure within the cranium is ocularly demonstrable by the flattening of the surface of the brain. But, even in inflammatory changes of the vessels within the cranium, it must be constantly kept in mind that the outflowing fluid can only have the effect of narrowing the cranial space from the moment when the efferent lymph channels can no longer suffice for the emptying.

We do not know whether in inflammation other factors than the pressure supplied by the heart are at work; there seems to me to be a possibility of this. I cannot imagine any adequate explanation as to the source whence the comparatively enormous pressure within a narrow artery and its area of distribution proceeds whenever inflammation attacks it. As every basis is wanting here, it would be inappropriate to discuss a subject which can only be treated *a priori.*

Let us now consider a further mechanical disturbance which, under pathological conditions, may take place in the cranial contents.

That *most of the bleedings from arteries* into the membranes

of the brain or into the brain itself have the effect of circumscribing the space in their vicinity, and that an escape of the contents of the ruptured artery will continue until the pressure which is exerted on the outer surface of the vessel has become equal to that on the inner surface, requires no further discussion. In the brain, the same thing happens exactly as elsewhere; only here, besides the symptoms of impairment of the activity of the organ generally, the peculiar symptoms also appear which belong to the part of the brain specially affected, so soon as its function is changed.

It is a fact, well founded on experience, that the severity of the general impairment is caused by the greater or less rapidity of the escape of blood, just as much as by the total quantity poured out. Both, of course, depend on the size of the rupture and on the blood pressure in the injured vessel. With this scanty general statement we must at present be satisfied;[1] so many indefinite factors have part in the matter under consideration—changes in the central nervous system affecting the respiration, the heart, and the vessels—that every case of ordinary cerebral hæmorrhage shows varying symptoms. Its fundamental feature, one-sided paralysis, remains, but general impairment of the function of the brain appears in various forms.

As regards therapeutic treatment, the general disturbance is the guide. But it is scarcely possible to speak of really intelligible rules to be necessarily deduced from the given conditions. If we start from the supposition, which in itself is not to be contradicted, that after a hæmorrhage into the brain all the symptoms of changed activity of this organ are to be ascribed to deficient nourishment, and this again to insufficient blood circulation, still nothing is gained. For it by no means directly follows that by means of *general* increased or diminished pressure of the blood, or of *general* acceleration or hindering of the rapidity of the blood-flow, we could come to the help of the individual organ, which is here the brain, still less that we could arrange what is necessary for this or that region lying within the whole organ, and which may be especially endangered by

[1] Compare the clear statements of Nothnagel, loc. cit. p. 93 et seq.

abnormal changes in its circulation. Thus our treatment is guided by chance more than by a clear insight into the nature of events, when, in treating apoplectics, we consider it imperative to increase or diminish the supply of blood to the brain—a mode of treatment, moreover, difficult to carry out.

This is especially true of venesection, in which, in the event of actual general lowering of the blood pressure being aimed at, large quantities of blood must be withdrawn.

Thus the importance of venesection in diseases of the brain would be based, not on a scientific, but only on an empiric foundation.

It may and must be admitted, that among the group of symptoms classed together as '*hyperæmia of the brain*' there are individual symptoms in which, under certain circumstances, venesection may be beneficial. Consider, for example, the case mentioned by Nothnagel,[1] who, after depletions to a small amount had been performed on a shoemaker suffering from intermittent delirium, saw gradual improvement set in. But here the decision of the physician must always be arrived at with the distinct consciousness that from one case to another he is making an experiment which may be successful or unsuccessful.

In true *inflammation* of the brain and its membranes, general depletion may be of as little use as in any other local inflammation.

Even in the treatment of *cerebral hæmorrhage*, venesection belongs to purely empirical remedies. It is quite true that sometimes a man, who, after a fit of apoplexy, lies in a state of profound unconsciousness, comes to himself immediately after venesection. It is therefore possible that such treatment may be of use.

Nothnagel[2] thus lays down the special indications, established by experience, for venesection after apoplexy:—'Turgescent face, perhaps also with distended veins, strong carotid pulsation; if the beat of the heart is strong, and the tension

[1] Loc. cit. p. 49.

[2] Loc. cit. p. 102. Hasse, who, however, speaks somewhat more cautiously, is of just the same opinion ('Krankheiten des Nervensystems,' in *Virchow's Handbuch*, 2nd edit. p. 442 et seq.)

in the radial artery at least normal, and if the pulse, whether slow or of normal frequency, is regular; if the respiration goes on in an even and quietly stertorous manner; and if the individual is strong, but not too old.'

If these conditions coexist, Nothnagel thinks that venesection is indicated, even in those circumstances 'in which the considerable pressure on the brain has already caused a commencing paralysis of the centres of the vagi (rapid pulse) and of the respiratory centre (Cheyne Stokes respiration). At least in such a case venesection, along with the simultaneous administration of stimulants, may preserve life.'

'In all cases which do not present this clinical picture venesection is unnecessary.' This concession with regard to venesection in apoplexy appears to me to go as far as is possible at the present day.

Setting aside my own experience I shall bring forward the statement of a physician who belongs to a period in which men were less cautious in drawing blood—viz. Trousseau [1] (in empirical subjects it is lawful to quote authorities). 'If in cerebral hæmorrhage I make use of neither venesection, nor purgatives, nor revulsives, it is because I know from experience that the patients are better without them.' In any case it ought not to be forgotten that, under the name of venesection, one wields a two-edged sword, and often a very small excess of depleted blood brings life itself into danger. So say the physicians who are regarded as authorities in these matters.

The condition of the circulation in the *lungs* is also peculiar. In the main, two circumstances must be brought prominently forward.

1. By means of the vital energy supplied by the respiratory muscles the lungs become extremely important organs in the promotion of the circulation. First of all, their activity helps the right side of the heart, but the systemic circulation also is aided in no inconsiderable degree. These conditions were lately thoroughly discussed by Diesterweg.[2] His quantitative estimates must be received with a certain amount of distrust, and they

[1] *Klinische Medicin*, translated by Culmann, vol. ii. p. 11 et seq.

[2] See especially *Ueber die Anwendung der Wellenlehre auf die Lehre vom kleinen Kreislauf*. Berlin, 1867, Hirschwald.

afford scarcely sufficient foundation for very exact calculations; still the importance of the movements of the lungs for the whole circulation has again been brought into notice in a manner which deserves our thanks. I believe that this may often have a more than theoretic interest for the physician.

2. The pulmonary artery is furnished in a very high degree with the capability of bearing a considerable decrease of the diameter of its efferent ramifications without a notable increase of the pressure in its trunk, and without any perceptible lessening of the blood flowing through it. Its walls are capable of great distension.

This fact has been firmly established by an experimental investigation into the normal condition of the circulation in healthy animals, carefully carried out by Lichtheim under Cohnheim's guidance.[1] It is therefore intelligible that the varying conditions, to which the pulmonary vessels are subject from the effect of the respiration, present no impediment to the circulation. It is not to be wondered at, and changes nothing of the main fact, that a less powerfully acting right ventricle, or diminished propulsive power of the respiratory act, no matter whence they proceed, should modify the results obtained in these experiments.

With respect to the object at present in view, it is only necessary to discuss the question, *What effect has a withdrawal of blood on œdema of the lungs?*

The *cause of œdema of the lungs* is by no means clear, even when we remember all the more or less well-constructed attempts at explanation. Experimental investigations appear only to show that an extremely complicated mechanism, and one which is capable of being affected from very different directions, comes under consideration; they have brought about final refutation of some long-prevailing opinions, and that is certainly a great point gained. Especially the doctrine of acute collateral hyperæmia, such as may lead to exudation of serous fluid, has become untenable. The experimental results obtained by Lichtheim agree exactly with all that observation, uninfluenced by prejudice, learns at the sick bed.

[1] *Die Störungen des Lungenkreislaufs und ihr Einfluss auf den Blutdruck.* Berlin, Hirschwald, 1876.

I cannot consider the researches of Welch,[1] and their very meritorious completion by Sigmund Mayer,[2] as being so decisive as actually to give us a clear insight into the pathogenesis of pulmonary œdema.

We may here treat of this subject more in detail. The results obtained by Welch are:—

1. Dogs and rabbits behave differently towards the mechanical conditions which engender pulmonary œdema. In rabbits there ensues a less degree of pulmonary œdema than in dogs.

2. In *rabbits* pulmonary œdema regularly appears whenever one carotid or the right subclavian forms the only opening, except the coronary arteries, by which the blood can escape from the aorta. In *dogs* pulmonary œdema is frequently only set up when every exit of blood from the aorta—the coronary arteries alone excepted—is closed. The outflow from the left side of the heart must always be more obstructed in dogs than in rabbits, in order that pulmonary œdema may be set up.

3. The pressure in the pulmonary artery is in a very high degree independent of the pressure in the aorta. It is only when the resistance in the systemic circulation has reached an enormous height that the pressure in the arteries of the lungs increases also—e.g. it has been observed to increase to $3\frac{1}{2}$ times the normal.

Welch himself thus concludes from these results:—

By ligature of the trunks of the arteries of the systemic circulation, an œdema of the lungs from stagnation can, but not necessarily must, be produced.

A considerable stagnation, however, of the blood in the lungs ensues, in consequence of increased resistance in the systemic circulation, only when this resistance has reached a degree which *in man it scarcely ever attains*.

A certain degree of stagnation in the lungs may exist without causing œdema.

In ligature of the pulmonary veins it was proved that—

1. Rabbits and dogs are not essentially different.

[1] 'Zur Pathologie der Lungenœdems,' *Virchow's Archiv*, vol. lxxii. 878.

[2] 'Bemerkungen zur Experimentalpathologie des Lungenœdems, *Sitzungsb. der k. k. Akad. der Wissenschaften*, vol. lxxvii. May 1878.

In order to produce pulmonary œdema an almost entire closure of the pulmonary veins must take place.

2. In spite of the increase of the pressure in the pulmonary artery, the pressure in the aorta remains comparatively constant. The pulmonary veins may be closed to at least three-fourths of their capacity, without the pressure in the carotid showing itself essentially influenced. It is not till a certain limit—which, however, is very high—has been exceeded that the pressure in the aorta falls.

The final result of this series of experiments is little adapted for application at the sick bed; for, with all the hindrances created to the outflow of the blood from the pulmonary veins into the left side of the heart, it was only when almost all the branches of the pulmonary veins were blocked that considerable increase of pressure in the pulmonary artery and œdema of the lungs appeared.

Welch, fully perceiving this, points out that the conditions under which he could produce pulmonary œdema differ very considerably from those which have to do with its production in man. He, however, maintains firmly that the œdema produced in his experiments results from stagnation, and asks accordingly whether there may not be other factors which can produce stagnation of the blood in the lungs and consequent œdema.

Welch answers the question thus:—

In *paralysis of the left side of the heart*, with a permanently sufficient activity of the right side of the heart during the paralysis, an accumulation of blood in the lungs may ensue, which is naturally sufficient to set up passive œdema in this organ.

To speak more definitely, a relative disproportion between the work of the left ventricle and that of the right signifies that, with the same continuous resistance, the left ventricle cannot expel the same quantity of blood in the same time as the right. Welch thinks that, in these circumstances, such a large quantity of blood must be forced out of the right ventricle into the pulmonary arteries that an accumulation of it takes place in the capillaries and veins of the lungs, until the quantity flowing out through the pulmonary veins has become the same as that impelled into the pulmonary arteries. It

must be premised that the blood conveyed to the right side of the heart is not less than before.

Experimentally, Welch produced pulmonary œdema in rabbits by mechanical stimulation—viz. squeezing—of the left ventricle. The pressure in the carotid sank considerably in consequence. The pressure in the pulmonary artery was not measured; there is found in the protocol of the experiment only the statement that the pulmonary artery, the right ventricle, and also the left auricle were distended, filled with blood, &c.

It must be observed that the experiment in many cases did not succeed. The heart suddenly stopped even after it had been comparatively slightly squeezed. Often both ventricles were in the same degree and at the same time enfeebled; it happened once that a squeeze, which proved to be rather too slight, acted directly as a stimulant to the muscle of the heart. Only the rabbit, which, by ligature of the branches of the aorta, gets pulmonary œdema much more easily than the dog, was suitable for these experiments. The dog, in the opinion of Welch, has a heart which has much too strong walls and is too powerful to be capable of being sufficiently squeezed by the pressure of the fingers.

To me this theory of Welch, ascribing the origin of the pulmonary œdema to greater work of the right ventricle, along with a paralysed left ventricle. appears extremely doubtful.

The fundamental principle may be repeated in few words.

There arises an insufficient activity of the left ventricle, so that it cannot empty itself of the blood contained in it. The consequence of this is that the blood cannot flow sufficiently quickly from the pulmonary veins into the left auricle. It thus remains within the lungs, and the right ventricle, entirely uninjured and normally active, now drives such a large quantity of blood into the lungs that finally the pressure within the capillaries is sufficient to force part of the blood through their walls.

Let us keep to the results of the experiments themselves.

1. As a constant condition in the successful experiments, we must expect a *great distension of the left ventricle* by blood, or else a *tetanic contraction* of it, which renders the entrance of blood impossible. Only in one of the successful experiments

(VIII.) Welch states that the heart may stop in systole; Experiments IX. and X. mention nothing of this.

2. Whence comes the propulsive force which conveys the necessary amount of blood to the right side of the heart, whenever the left side stops its work entirely or for the most part? In the experiments of Welch we find 20 mm., 30 mm., indeed tolerably rapid sinking down to 0 mm., noted in reference to the pressure in the carotid. According to all that we know of the circulation, the consequence of this must be a hindering of the blood current to the right side of the heart. With perfect justice, Sigmund Mayer remarks that Welch passes over this important point more lightly than is desirable. Before I discuss more minutely the extended investigations of Mayer, especially directed to this side of the question, I should like to mention another difficulty.

3. When, as a result of the squeezing of the left ventricle, the pressure within the carotid falls so very much, as it did, it is certainly very improbable that the flow of blood to the heart itself through the coronary arteries remains unchanged. It is therefore not at all probable that, with a pressure in the carotid amounting to a few millimetres, the right ventricle, which pulsates for several minutes longer, should be working with unimpaired power. Here no mere appearance is enough; direct measurement of the pressure in the pulmonary artery is required.

Before I proceed further, I wish to take up the experiments of Sigmund Mayer.

Mayer, who experimented exclusively on rabbits, brings prominently into view the essential difference which exists between curarised animals, in which life is maintained by artificial respiration, on the one hand, and non-curarised animals, whose respiration is natural, on the other.

In the great majority of the non-curarised rabbits, very well-marked œdema of the lungs appeared so soon as the arteries from which the brain derives its blood (innominate and left subclavian) were ligatured, and the animal, in consequence of the anæmia of the brain thus produced, suffered from violent convulsions. In the case of curarised rabbits, œdema of the lungs does not, under the same experimental conditions, take place.

The œdema thus originated, Mayer thinks, proceeds in the main from stagnation, in Welch's acceptation of the term; for he considers it not very probable that, by simple closure of the arteries going to the brain, any change whatever worthy of notice would, after the lapse of so short a time, take place in the blood or in the walls of the vessels.

Firmly adhering to the supposition that, under these conditions, pulmonary œdema has arisen from the stagnation, Mayer enlarges on the question, which has been but superficially treated by Welch, with regard to the nature of the propulsive powers which could convey a sufficient quantity of blood to the right ventricle after more or less complete paralysis of the left. For this purpose the case of the non-curarised rabbit is made the basis of his remarks. It is distinctly stated—

The closure of the large arterial trunks passing to the brain acts at first as a purely mechanical hindrance to the outflow of blood from the aorta, and, farther back, from the left side of the heart and the pulmonary veins.

The central nervous system is thus acted on, and causes such a powerful contraction of the small arteries of the systemic circulation that these—at all events the majority of them—must be regarded as almost entirely closed. The central irritation of the vasomotor nerves results from the cerebral anæmia. Thus a new obstacle to the emptying of the left ventricle presents itself.

At the same time the powerful contraction of the arterial wall exercises an immediate propulsive force on the blood contained within the narrowing vessels, which is propelled into the veins and consequently towards the right ventricle. Cerebral anæmia, however, sets free still more 'accessory' forces to aid the movement of the blood towards the right ventricle.

The strong respiratory movements in cerebral anæmia have considerable effect—inspiration by increasing the suction power of the right side of the heart to a degree far exceeding its usual power; expiration by exercising, by means of strong contraction of the abdominal muscles, a pressure on the large venous trunks situated in the abdomen, which propels the blood in them towards the right side of the heart.

The contractions of the muscles, which in cerebral anæmia

quickly pass into the form of convulsions, conduce to a removal of the venous blood contained in them, once again, by driving it in the direction of the right side of the heart. By means of the strong tension of all the muscles co-operating in the abdominal pressure, the emptying of the large trunks in the abdomen is again promoted in a considerable degree. These sources of force are, however, not equal in value. Mayer gives great prominence to the suction power of the thorax and the contractions of the voluntary muscles, particularly the action of abdominal pressure ; to these he ascribes the greatest importance. This opinion he again supports by an experimentally discovered fact.

A non-curarised rabbit, after closure of the arteries supplying the brain, suffered no pulmonary œdema so soon as the abdominal pressure was rendered inactive by opening the abdominal cavity in the middle line, the double-sided pneumothorax thus produced being compensated by artificial respiration. In this experiment, the non-striped muscles of the arteries, along with the mechanical squeezing of the muscles during their contraction, were active as an 'accessory force' in promoting the movement of the blood to the right side of the heart. These alone, however, are by no means sufficient to bring about local movement of the blood in sufficient abundance.

So much for Mayer. Even with the extended information given by him, there appears to me to be no proof at all adduced that the œdema observed by him and Welch really took place in the manner supposed. For let it only be remembered that about three-fourths of the veins passing from the lungs may be closed without causing any noteworthy diminution of the pressure of the blood-receiving system of the aorta ; almost all the veins of the lungs must be closed before *pulmonary œdema* appears, and such is also nearly the case with regard to the arterial portion of the pulmonary circulation. Thus, then, with the pulmonary vessels a very great amount of adaptability to varying circumstances is possible, and their diameter must be susceptible of enormous enlargement. Notwithstanding this, a right ventricle, in all probability not perfectly capable of work, to which—at least in the experiments of Welch on curarised animals—doubtful quantities of blood are conveyed,

is capable of causing so high a degree of pressure in the capillaries of the lungs as to cause œdema. To this it may be added, that Welch was not by any means always able to produce pulmonary œdema by squeezing the left ventricle; Mayer caused no direct injury to it, and yet saw, with rare exceptions, the appearance of pulmonary œdema after cerebral anæmia. An overfilling of the left ventricle with blood, or tetanus of the ventricle, is not reported in these experiments, and the pressure in the pulmonary artery was not measured; and therefore no proof in favour of an increase of pressure has been adduced. When we say, therefore, that these experiments themselves require explanation, and that the mechanism of the cause of pulmonary œdema is not sufficiently cleared up by them, we utter an opinion considerably within the bounds of moderate criticism.

An unintelligible fact must not be used to explain another equally unintelligible. For the present, therefore, these facts, obtained by experiment and requiring to be judged by themselves, are not to be taken into account when an opinion is to be passed on what comes before the notice of the physician at the sick bed.

Observation of the conditions under which pulmonary œdema shows itself in man, proves that here a mere mechanical cause, which in all circumstances must lead to the same final result, is by no means necessarily to be taken for granted. Almost without exception conditions are present here which render probable a less satisfactory nutrition of the vessels in general and of the pulmonary vessels, or a part of them, in particular, and thus furnish to scientific intelligence an addition to the good and firmly-established doctrines on the influence of the wall of the vessel on the exit of its contents. If experimental pathology desire direct application of the results it has obtained, then it remains for it to fulfil the task of putting it to the test whether, with insufficient nutrition of the vessels in the lungs and with inflammatory changes in them, a closure of the exit of the blood from the lungs is really possible to the same extent as in normal animals, without causing the appearance of œdema. We are justified in doubting, until a proof of this can be adduced. For, as has been said, among the condi-

tions that come under our observation, insufficient nutrition of the vessels is almost always probable or certain. Proofs of this might be given in abundance.

In what respects are the conditions in croupous pneumonia changed as compared with the normal state? Diminution of a part of the pulmonary space, decrease of the propulsive power furnished by the respiratory muscles to the blood, direct impairment of the power of the active muscles—of the heart in particular—in consequence of fever, imperfect removal of the waste products of tissue metamorphosis with insufficient renewal of the material used by the body, by supply from without; and, as anatomical indications of the injury to the tissue, signs of parenchymatous degeneration. These are the prevailing conditions in this case. Is it, therefore, to be expected that the vessels of the lungs will remain entirely free from the general depression?

How is it in pulmonary emphysema with weakness of the heart that it is a matter of indifference what anatomical changes are present in the organ? No one in these circumstances hesitates to ascribe the dropsical exudations, anasarca, ascites, and hydrothorax, to insufficient nutrition of the walls of the vessels. Why, then, should so separate a place be assigned to pulmonary œdema with so acute a course? I will not digress too much, and only call to mind the well-known fact, that pulmonary œdema is recognised as the final result of the whole process in acute febrile conditions—pneumonia—in an overwhelming majority of cases near the end of the characteristic fever, in chronic diseases of the lungs—emphysema—at the time when a catarrh of the bronchi prevails, which implies a condition accompanied by inflammatory changes of the vessels. I may further remark that, in the dependent parts of the lungs, those in which the force of gravity resists rather than promotes the circulation, œdema with congestion, as a rule, ensues.

There appears to me, after all, only a small number of cases remaining, in which subordination to the general rule presents difficulties—such cases as œdema after sunstroke or after poisoning with carbonic oxide.

It need not cause surprise that pulmonary œdema does not always appear under apparently similar mechanical conditions;

for the unascertainable conditions of individual tissue nutrition must be taken into account. On the contrary, we do justice to these considerations so soon as we say with Cohnheim[1] that 'the accidental inconstancy in the appearance of pulmonary œdema is an argument against its having its origin in purely mechanical conditions.' I also wish directly from the standpoint of the therapeutist urgently to recommend for consideration another statement of Cohnheim's:—

'*Men do not die because they have pulmonary œdema, but they acquire pulmonary œdema because they are about to die.*'

This is a perfectly warranted generalisation of that which I brought forward, but did not so pithily express, in reference to croupous pneumonia when discussing the therapeutics of this disease; and it has, in Cohnheim's conception, attained its full value by inculcating the necessity of not reckoning with what has already taken place and of firing against it heavy artillery—for the most part useless—but of watching what is actually taking place, and as far as possible of inclining us to the idea that, given sufficient activity of the heart, then sufficient circulation of the blood takes place.

Thus prophylaxis is, in the main, the duty of the physician.

But pulmonary œdema often comes on very suddenly in an extremely violent form, literally flooding the lungs with transudation, and in this case active treatment is necessary. Then our task is to effect the disappearance of the œdema in as short a time as possible.

Withdrawal of blood *may*, in certain circumstances, be the only means, the application of which can preserve a life in extreme danger. *But it should only be practised when, in very deed, no time is to be lost and every other way is closed.*

In my opinion, in attacks of œdema, such as occur in croupous pneumonia, pleurisy, often also in miliary tuberculosis, but most frequently in acute infectious diseases in the stricter sense of the word, there is *always* to be found *feebleness of the heart*, which frequently comes on very suddenly, and which betrays itself by the arteries becoming more empty and the

[1] *Vorlesungen über allgemeine Pathologie*, p. 420.

veins fuller. The greatest variations exist as to the manner in which the heart is impaired. Sometimes innumerable powerless contractions are felt, which occasionally vary so much in their strength that, along with a series of scarcely perceptible radial pulsations, a few very considerable dilatations of this artery are felt, and then only the half of the normal beats of the pulse can take place. The final result is always the same, viz. change in the distribution of blood in a sense the opposite of its normal condition. With regard to the systemic circulation, this admits of no well-founded doubt; even without direct measurement of the blood pressure the conditions here are perfectly clear. In favour of the opinion advocated by me, that even insufficient activity of the *right* side of the heart is enough, when a person is unwell, to set up pulmonary œdema, and in fact an œdema proceeding from stasis, I would once more suggest that the vessels in those cases of pulmonary œdema which we see at the sick bed *are not under normal conditions of nutrition.* The experiments on animals as performed by Welch cannot therefore be regarded as decisive.

Besides, I must remark that in post-mortem examinations of bodies which present signs of a high degree of pulmonary œdema, we find as a rule the right side of the heart and the large venous trunks of the systemic circulation entirely filled with blood, while the left side is found to be neither firmly contracted nor engorged with blood.

Finally, it should also be remarked that unequal action of the two sides of the heart is indeed sometimes certainly observed (Leyden), but in pulmonary œdema clinical indications of it have not hitherto been found.

The therapeutical core of the question—what effect general bleeding has in pulmonary œdema—is indeed in this discussion but little touched on.

If we share the belief of Welch and Mayer, then it must be said that a large depletion by venesection diminishes the quantity of blood conveyed to the right side of the heart, and thus it is impossible that such a quantity of blood can be driven from the right side of the heart into the lungs as that stasis should ensue.

According to the opinion hitherto received it is believed

that a diminution of the blood accumulated in the veins of the systemic circulation conduces to a diminution of the resistance offered to the left side of the heart, and to a temporary relief of the right side, as the quantity of blood to be driven onwards by it will be less. Thus the blood entering the right side of the heart under higher pressure will be driven onwards to the left in shorter time.

A belief common to both these opinions is that the absorption of the œdematous exudation is promoted by the rapid depletion of blood, for which absorption the easier emptying of the large lymph channels, brought about by the diminished pressure in the large venous trunks, is also of some consequence. Often—not by any means always—we see the respiratory muscles attain to powerful action during and after venesection, so as considerably to aid the action of the heart by their energy. This has some connection with changes of the irritability of their cerebral centres—changes which are not more precisely known.

As the effect of a withdrawal of blood in these circumstances appears to be theoretically intelligible, so also experience teaches that venesection is capable for a certain period of averting the danger directly threatening life, a period varying in individual cases. *How much blood* must be withdrawn, cannot be stated generally, but we may venture to say that whatever is to be withdrawn must be taken from the *veins* and in as short a time as possible ; for in that way the mechanical effects of a withdrawal of blood are attained with the smallest loss. The consequent loss in living tissue, in blood itself, and in formed constituents, which are disintegrated as a result of the loss of blood, is restricted to what cannot be avoided.

In these injuries, inseparably connected with every depletion, lies the shady side of the whole proceeding. The body, after the loss of blood, has less power of resistance than before. If the disease continues, and if the conditions which called for the first venesection do not change, then the situation is generally in a short time the same as it was before. The weakening effect of the disease, however, is evidently much strengthened by every repetition of the operation ; for this reason, that the number of red blood-corpuscles in a given volume of blood is

still more diminished, and only increased activity of the muscular system—the heart and respiratory muscles—can cover the deficiency, by more rapid circulation of those that are left. These muscles, however, notwithstanding increased activity, are repaired and restored always more and more insufficiently, and thus the time of final decay cannot be long delayed.

This is not the place to go into the foundation of the treatment which renders withdrawal of blood unnecessary even in these conditions, or which at least confines it to extreme cases. I refer the reader to what I have already said in discussing the therapeutic treatment of pneumonia.

Further indications for the withdrawal of blood will be discussed in the following section, to which they more properly belong, as we are considering here only temporary, not permanent diminution of the quantity of the blood.

We are now at the end of our journey. The conservative tendency of the therapeutics of the present day shows itself in the domain of medicine as well as that of surgery.

Every physician, who is accustomed to consider the blood as an organ of the body, will ask himself whether in reality the welfare of the whole body requires the sacrifice of a part. He will make such a sacrifice only when it is needed in order to carry out the chief task of the therapeutist, viz. to assure the continuance of life itself.

The waste of blood of a not very distant past is, let us hope, for ever gone. The possibility remains that deeper research into physiological and pathological conditions may place the therapeutic application of venesection within wider bounds than can at present be fixed.

TRANSFUSION.

The *history* of transfusion has been repeatedly dealt with so exhaustively that, in order to fulfil the duty required here, it is sufficient to give a short sketch of it. Whoever wishes to learn further particulars will find an excellent account in the work of Paul Scheel, and its continuation by Dieffenbach.[1] Landois[2] has lately produced a careful historical research, based on original study, the results of which in the main coincide with those obtained by Scheel. The original works are rare in German libraries, and his extremely careful labour has been rewarded with but scanty profit. The agreement of these authors affords a proof that everything worth knowing is known. I therefore abandon the idea of giving an account of the literature of transfusion. It will be found in the works just mentioned.

Scheel took up as the first section of the history of transfusion the period from the time when uncertain traces of the operation appeared until the first experiments after the discovery of the circulation of the blood. The literature of that period is exactly that which Landois has more closely reviewed, and to which he has devoted a chapter of his second work well worth reading.

It is not in the works of Magnus Pegelius, born at Rostock in 1547, and afterwards Professor of Mathematics at the University there, but in the writings of Hieronymus Cardanus, born at Pavia in 1501, that Landois finds, in opposition to Scheel, the

[1] *Die Transfusion des Blutes und Einsprützung der Arzeneyen in die Adern*, 2 parts, 1802 and 1803, Copenhagen, Brumann. Continued by Dieffenbach, Berlin, Enslin, 1828.

[2] (a) *Die Transfusion des Blutes*—the principal work Leipzig, Vogel, 1875: (b) 'Beiträge zur Transfusion des Blutes,' Leipzig, Vogel, 1878, reprint from the *Deutsche Zeitschrift für Chirurgie*, vol. ix.

first published traces of the idea of transfusing blood from the vessel of one individual into that of another. A method, which, though feasible, was not then practised, is described by Andreas Libavius, born at Halle in 1540, in his work which appeared in 1615 ('Appendix necessaria Syntagmatis Arcanorum Chymicorum'). It is there said—

'Magister artis habeat tubulos argenteos inter se congruentes. Aperiat arteriam robusti (juvenis) et tubulum inserat muniatque; mox et ægroti arteriam findat et tubulum fœmineum infingat. Tum duos tubulos sibi mutuo applicet, et ex sano sanguis arterialis calens et spirituosus saliet in ægrotum.'

Libavius himself, it is true, scoffs at this proceeding; but it may be inferred with certainty from the passage just quoted that, even before they had acquired accurate knowledge of the circulation, physicians had at least made themselves theoretically familiar with the idea of a direct transfusion of blood.

Nevertheless from the time of the appearance of that publication of Harvey, which, in 1628, revealed the discovery of a complete circulation of the blood, nearly forty years elapsed before transfusion of blood was undertaken in man.

The *second* section of the history of transfusion, beginning at that time, extends to about the twentieth year of the present century.

The scientifically important questions, which come under consideration, had been already to a great degree started by English investigators, and, what is still more, they had even been previously decided by experiment. In France everything remained an empty show, from which single individuals in their own interest drew a profit; the gain to science was therefore but small.

It was only a short gleam of sunlight. From 1665 to 1668, with the help of the Royal Society of London, a series of experiments was set on foot which, being undertaken by temperate observers, appeared to give fair promise of success. Thus Lower, the renowned anatomist, found that a dog, nearly bled to death, could be revived and recovered permanently by direct transfusion of blood taken from another dog. This experiment was repeated and confirmed before the Society. A commission from its members was appointed by the Society, and two of the

commissioners, Drs. Coxe and King, repeated the experiment of Lower at a public meeting. It was Lower also who conveyed the blood of a dog from its crural artery into its jugular vein.

Along with these investigations, which were perfectly in accord with the ideas of later centuries, others soon appeared, which, being the growth of their time, must not be unreasonably condemned, but to which must certainly be imputed the blame of causing transfusion to be again forgotten. The old opinion, 'Blood is life,' hedged round with the scholastic dogmas of the time, lies at the foundation of all these errors. Thus, in the problems which Robert Boyle proposed to the Society for solution, this highly intelligent man asked whether *old animals could be made young by transfusion and young ones could be made old.* He stood in the midst of indisputed opinions when he asked, as a problem to be solved by experiment, '*Is it possible, by repeated transfusion, to change an animal into one of another species?*' The unfavourable result of all this was, that in England men proceeded to practise transfusions from one species to another, and by this means they lost the right foundation for its therapeutic application and opened a wide door for the intrusion of all kinds of mystical ideas. This happened about the end of the year 1666.

The news of the English experiments seems quickly to have penetrated into France; for, on March 31, 1667, Denis, with his expert operator Emmerez, took up the experiments of the English. At first reciprocal transfusion among dogs was tried; and then, after transfusion of a calf's blood into dogs had proved successful, the first transfusion of a lamb's blood into human beings was made on June 15, 1667. Denis even preferred animal to human blood. These were now followed, until the end of the year, by several similar operations, which were partly successful, when the death of Antoine Mauroy, which in all probability had no connection with transfusion, closed the series. How that happened, and why it was that Denis, who came forth victorious from the judicial examination, abandoned the practice of transfusion, seems not to be satisfactorily explained. Scheel thinks that Denis, having been most violently attacked and becoming weary of the strife, had thought it better 'as doctor of medicine and Royal Physician quietly to practise the thera-

peutics of his day than to become a martyr in the cause of transfusion.'

It appears that the occurrences in Paris had thrown shadows far beyond the bounds of France; for even in London experiments relating to transfusion died out after the direct transfusion of lamb's blood had been thrice practised on a somewhat crack-brained but otherwise healthy Bachelor of Theology (at the end of 1667), without, however, restoring his normal cerebral function. Transfusion was, however, performed elsewhere in the following years: in Germany by Kaufmann, 1668; in Italy by Riva and Paulus Manfredus, 1667–68; but, in the main, transfusion was forgotten and went out of fashion. Even the careful experiments on animals of Rosa (1783), Professor in the Medical Faculty at Modena, made no great impression on his contemporaries.

Important experiments made by Bichat form the transition to the third period, which contains more minute investigations into the conditions coming under consideration in transfusion. This investigator did not lay himself out to make transfusion his peculiar study, but he employed this method in his researches into the action of arterial and venous blood on the brain. In these researches he practised both direct and indirect transfusion—the latter with the help of a syringe, yet without previous defibrination of the blood. Indirect transfusion had also been already practised by Timothy Clarke, one of the first English investigators, in the year 1657.

This kind of transfusion was first brought into common use by James Blundell, who since the year 1819 had injected non-defibrinated human blood into the veins of those who were bleeding to death; and out of seven patients operated on, according to the summaries in Landois's works, he was successful in three cases. He even ventured on the operation in a case of puerperal fever with extreme exhaustion, which, however, ended in death. Blundell certainly deserves the praise bestowed on him by Landois, that, by the use of the syringe, he has brought the whole operation so very much nearer to being one which we can carry out in practice. The results of his experiments on animals also deserve notice. Now follow the highly im-

portant works[1] of Prevost and Dumas in 1821; of Dieffenbach, 1828; of Bischoff, 1835; of Magendie, 1842; of Brown-Séquard, 1858; then the comprehensive work of Panum, 1863, combining with an intimate knowledge of the literature of the subject a great number of most careful experiments, the results of which form one of the main foundations of the theory and practice of transfusion. Not so important, but still worthy of notice, are the studies of Eulenburg and Landois, 1866; of less importance still, the work of Belina-Swioutkowski, 1869.

It seemed as if the doctrine of transfusion, theoretically well established by the above-named works and many smaller ones, had prepared a fertile soil for the practice of it. The number of cases in which the operation was performed increased from year to year, and slowly and steadily it made its way. But a torrent burst out—only for a short time, it is true—which, rejecting the results of physiological investigation, threatened to toss everything back on the rock of simple empiricism. It was not the publications of the enthusiast Gesellius, who with high-sounding words promised 'a new blood-distributing era,' but rather the pretended success of Dr. Hasse, of Nordhausen, 1874, which gave a new impetus to the direct transfusion of blood from sheep or lambs, in opposition to the practice hitherto used of indirect transfusion of human blood into human beings. Dr. Hasse was known in distinguished circles as a highly honourable though somewhat sanguine man. At the same time the success which he asserted he had attained by means of the direct transfusion of lamb's blood in phthisical patients was attractive enough: the *crux medicorum* might perhaps be accessible to therapeutics, and physicians began in many places to test Hasse's proceedings.

That the nimbus very soon disappeared is a well-known fact. The renewed investigations of physiologists contributed not a little to this, and more especially those of Landois, who, in the end of 1873, communicated a short account of his experimental results, a thorough exposition of which is given in the work already mentioned, which comprehends the whole sub-

[1] The year of the publication of the works is given. The experiments of the various investigators often extended over a number of years; e.g. those of Panum began in 1854.

ject of the doctrine of transfusion. Ponfick also, in 1875, published a series of experiments, which, in perfect agreement with those of Landois, lead to the conclusion that transfusion of blood from a different species is inadvisable. Panum[1] in two lucid and well-written treatises led the van in the discussion against the transfusion of lamb's blood. The physicians also who still continued to practise it were soon undeceived, and turned away from the treatment which had sprung up with such fair promise; and now it is hardly even spoken of.

As an important addition to the publications on transfusion may be mentioned the recent works of Lesser and Worm-Müller, particularly alluded to in the foregoing section.

The therapeutic aim, which hitherto has been associated with the transfusion of blood, is to renew to the receiver the blood that he has lost, or to improve the condition of his blood by mixing it with fresh blood.

It cannot be wondered at that diseased conditions of very different kinds were treated by transfusion. It is to be remembered that in the course of time very varying properties have been ascribed to the blood. The opponents of transfusion in the seventeenth century little needed to fear bringing ridicule on themselves, when in all earnestness they objected that, after the infusion of calf's blood, horns might grow on a man, and when the adherents to the opinions of their time ventured to harbour the expectation, that a lunatic could be cured of his madness by the injection of lamb's blood.

Only the knowledge of the actual work of the blood in the animal economy permitted of definite ideas on the possible use of blood renewal. The old axiom 'Blood is life,' with all the mystical ideas connected with it, has been compelled to give way to the simpler one 'Without blood no life.' In warm-blooded animals at least, the activity of all the organs, particularly of the nervous centres, is so closely connected with the presence of blood in its normal condition, that the withdrawal, even for a comparatively short time, of the blood supply is sufficient to destroy them permanently—to allow death to ensue.

We now know that the blood does not give compensation to

[1] *Virchow's Archiv*, vols. lxiii. and lxvi.

the body directly from its own substance, which, being a fluid tissue, has to be preserved like every other tissue. The blood, however, serves as a medium for the conveyance of nutriment to the tissues and for the discharge of waste, to the widest extent.

Among the constituents of the blood, the red blood-corpuscles are most prominently connected with the actions of the whole organism. Without them no exchange of gases is possible, which could in a given time supply sufficient oxygen and remove the carbonic acid which has been formed. The normal activity of the red blood-corpuscles is so allied with this absorption and discharge of gas that the chemically active hæmoglobin is combined in a precise manner with the tissue or stroma of the corpuscle. If this union is disturbed, the hæmoglobin, chemically unaltered, separates from the stroma, and then the function of the red corpuscle ceases; the hæmoglobin, having in a short time lost its activity, and sometimes having undergone more or less of chemical change, leaves the circulation.

These are facts which must be accepted as certainly correct. If they are made the basis of discussions of the doctrine of transfusion, then a definite standpoint is found, from which free survey on all sides is possible.

The discussion of the question must now be attempted—'*What conditions must be avoided in order not to injure the vital qualities of the blood in its transmission from one person to another?*' The standard for judging these is thus laid down: that the receiver who has been to a greater or less extent deprived of blood normally belonging to him may continue to live by means of the injected blood without any perceptible impairment of his general health; or, that such diseased conditions as are already present may be removed by the new blood infused, better and in a shorter time than would otherwise have been the case. Along with this there comes under consideration an extremely valuable proceeding as a preliminary experiment. Separation of the hæmoglobin from the stroma implies the death of the red blood-corpuscle. The liberated hæmoglobin passes into the plasma or serum, and colours it red. If, therefore, blood be mixed with a fluid, which by itself exerts no solvent action on the red blood-corpuscles, and if the fluid, after intimate mixture

with the blood, becomes coloured red, then it is proved that a dissolution of the red blood-corpuscles has previously taken place. The same conclusion may be drawn as soon as, in spontaneous coagulation, the otherwise colourless serum pressed out from the blood clot appears to be deeply reddened. Landois,[1] who has recommended the method, mixes equal volumes of blood and a solution of sulphate of soda, and shakes and filters them. The blood corpuscles remain on the filter; the filtrate does not coagulate. He then obtains an approximatively quantitative estimation of the dissolved hæmoglobin by comparison with a normal scale, as in Welcker's method.

The simplest conditions are presented when the transfusion of blood from one individual into another belonging to the same species is to be effected. The investigations on this subject have now proved that *it is not necessary to conduct the blood direct from the vascular system of one person into that of another. The blood taken from the one may be allowed to remain for a certain time out of the body without the red blood-corpuscles losing their function. So also stirring of the blood, for the purpose of removing its fibrin, does not to any extent impair the vitality of the red blood-corpuscles.*

The question discussed is of decisive importance in the practical application of transfusion. If blood required to be transfused directly from vessel to vessel, then the cases in which the operation could be said to be practicable must be sought with the lantern of Diogenes. To transfuse blood from the veins of one man into those of another is a venturesome undertaking, in spite of the comparatively slow coagulation of human blood. It is difficult to give any sufficient security against the formation and introduction of coagula into the circulation of the person who receives the blood. The want of rapidity of the venous current and its low pressure present great obstacles to the operation.

On the other hand the exposure of an artery—say, the radial—and its ligature, and the necessary operations connected therewith, is not an entirely safe proceeding. At all events such an operation presupposes great care of the part of the body operated

[1] Loc. cit. pp. 43, 44.

on for at least some days. The possibility of actual injury being done, may, as experience teaches, unhesitatingly be maintained. Who would consider a venesection of the same importance as the ligature of an artery?

Yet protests are raised from various quarters—less against the temporary removal of blood from the living body than against its defibrination.

Scarcely anything worthy of mention can in fact be brought forward, if the capability of the red blood-corpuscles to keep themselves uninjured for a time after their removal from the living body is to be disputed. It is sufficient, in refutation, to refer to Panum's experiments, only one of which I quote with all brevity (Experiments 9–11 of the original work mentioned).

A young dog, about two or three months old, whose weight at the beginning of the experiment was 2,420 grms.

Withdrawn from the animal—

August 18.	August 20.	August 23.
330·8 grms.	265·07 grms.	267·7 grms.

The blood on these occasions was replaced by the defibrinated blood of another dog to this extent:—

301·3 grms.	253·05 grms.	265 92 grms.

The weight of the dog then became—

2,420 grms.	2,210 grms.	2,290 grms.

The residue of its own blood, which the animal at the end of the series of operations still possessed, might be estimated at about 0·5 grm., or 0·3 per cent. of the whole quantity it possessed at the beginning of the experiment.

With the great diminution of fibrin which of course took place after each transfusion, nothing was apparently lost of what was necessary for the well-being of the whole organism and the undisturbed continuance of its functions.

The quantity of fibrin in the blood amounted to, at the beginning of the transfusion—

August 18.	August 20.	August 23.
2·4 per 1,000.	2·53 per 1,000.	2·57 per 1,000.

At the end of it—

0·75 per 1,000.	0·34 per 1,000.	0·47 per 1,000.

On the whole, in the three series of experiments, thirteen venesections and thirteen injections of blood were practised. On August 28 the animal was killed. Notwithstanding a necrosis of the bone of one of its legs, which had led to fracture of the bone, necessitating amputation, it was quite lively till the last day of its life.

In view of such experimental results, it is from a practical point of view of little importance that a small part of the red blood-corpuscles is by defibrination always destroyed. Landois has made experiments on this point which appear to authorise this conclusion. I here quote one of them [1] (37th experiment of the original).

Dog of 19,200 grms.; repeated blood-letting from the external jugular vein. The blood withdrawn was defibrinated and injected into the femoral artery of the same animal in the direction of the blood current.

Estimated weight of the blood, 1,476 grms. ($\frac{1}{13}$th of the whole weight of the body).

1. Venesection of 436 grms.
2. Venesection of 280 grms.
3. Venesection of 210 grms.

At intervals of half an hour. How long time was expended in each operation is not mentioned, nor yet the time in the two following:—

4. Venesection of 200 grms.
5. Venesection of 196 grms.

Quantity of blood withdrawn, then defibrinated and again injected = 1,322 grms. Besides this, 150 grms. were lost; thus the animal lost about 10 per cent. of its original quantity. The serum of the blood withdrawn in the five venesections contained blood-colouring matter dissolved in it. Landois estimates that the red blood-corpuscles contained in about 110 grms. of blood were destroyed; that is about 7 per cent. of the original quantity. If we remember how much the blood corpuscle is beaten about in the course of defibrination, its great resistance is remarkable.

I shall come back to this experiment in another connection,

[1] Loc. cit. p. 94 et seq.

but must remark here that next morning the animal was found dead.

Landois speaks of another possible injury of the red blood-corpuscle. He remarks 'that it cannot be definitely ascertained whether the whole of the blood corpuscles, though keeping in good preservation morphologically during the whole operation of defibrination and the long stay out of the body, may not perhaps fall into a state of slightly enfeebled vitality, even though only temporary, and after their return into the body quickly recover without any permanent damage.' I will honestly confess that I can form no distinct idea as to what Landois here really means. If I am to imagine something concrete, then it can only be a loosening of the union between the stroma and the hæmoglobin, somewhat as if an unequal distribution of the hæmoglobin diffused throughout the stroma had taken place in the blood corpuscle, thereby reducing the surface of contact between the hæmoglobin and the oxygen.

Another positive statement of the same investigator is, on the other hand, more important—indeed, of very great consequence. Landois [1] found that the stroma of the broken-up red blood-corpuscles can mechanically unite to form a tough, viscid mass, which, being very like fibrin, has received from him the name of 'stroma-fibrin.' The stroma-fibrin, driven round in the circulation, comports itself as a foreign body within the vessels ; it may remain anywhere as an embolus, and serve as a nucleus for the formation of thrombi. As some blood corpuscles are always destroyed by defibrination, there is at least theoretically a possibility that the stroma-fibrin formed from them may become hurtful.

This observation of Landois affords a suitable transition to a discussion of the opinions of those who consider defibrination of the blood in itself injurious.

At the head stands Magendie, who believed that the fibrin gives the blood a greater viscosity, so that the blood corpuscles slide through vessels of the smallest calibre more easily.

This opinion was founded on the blood-serum exudations (first mentioned by Magendie), which, after the transfusion of defibrinated blood, here and there occur—sanguineous œdema

[1] See below, where it is more fully treated of.

of the lungs, hæmorrhagic exudations into the intestines, injection of the capillaries, especially those of the intestinal mucous membrane, and more rarely of the stomach.

Panum, who also observed these effects, gave a different interpretation (see Experiment 8). He thought that in animals, from which as much blood was withdrawn as would flow from the carotid, extremely severe shocks to the nervous system occurred. It would be too much to expect that a dog, six weeks old (Experiment 8), should be able to bear being bled almost to death twice in the course of a few hours, and being twice recalled to life by the transfusion of defibrinated blood, without at least really dying the third time. The hæmorrhage from the mucous membrane of the intestines is, according to Panum, satisfactorily explained by the effect of the alternate weakening or paralysis of the heart after the bleedings and its vigorous action after the transfusions. 'For it is well known that, in stoppage of the heart, the blood pressure is so distributed that it rises in the veins while it falls in the arteries. When the heart, after having ceased to beat for a time, begins again to act powerfully, the pressure in the arteries must rise quickly and strongly; and, as the pressure of the blood in the veins is increased, the capillaries must be very much distended by the further violent activity of the heart; and it is then conceivable that hæmorrhage, especially in the mucous membrane of the intestines, may easily ensue, because the blood which flows into its small arteries has to overcome the resistance of two networks of capillaries, one in the intestines and the other in the liver. It is besides not inconceivable that the appearance, to at least a certain extent, of partial coagulation in the capillaries of the intestines may be produced during the continuous weakness, nearly approximating to stoppage, of the heart's action. In favour of this idea we may refer to the singularly small quantity of fibrin found in the second withdrawal of blood.' [1]

In proof of his opinion Panum remarks that in later experiments in which the transfusions were less hasty, though accompanied with a more copious withdrawal and injection of blood, serious symptoms did not show themselves.

[1] Panum in *Virchow's Archiv*, vol. lxiii.; p. 44 of the separate reprint; also in principal work, p. 170.

Ponfick[1] inclines to the belief that the hæmorrhagic extravasations, now and then observed by Magendie and others, were more the effects of accident than necessary adjuncts of the operation of transfusion—'little mischances' produced by a too hasty and uneven injection of the fluid, such as may only too easily happen in the hurry of the moment with animals bleeding to death. Ponfick could produce hæmorrhages at will by a very impetuous use of the syringe. Besides, we may think of emboli from the presence of foreign bodies, air bubbles, impurities introduced from without, in the injected blood, or from coarse coagula which form in the cannula of the syringe.

Landois[2] believes that some fine particles of fibrin may always remain in the defibrinated and strained blood. They, and the stroma-fibrin which springs from the disintegration of the red blood-corpuscles, may conduce to the formation of capillary emboli in the lungs and, if they can penetrate their network of fine vessels, also in the intestines and stomach.

The hæmorrhagic extravasations mentioned by Magendie formed the central point around which discussions on the applicability of defibrinated blood revolved. The explanation given by the French investigator was generally abandoned; a satisfactory explanation of the appearance of the phenomenon, only exceptionally observed by him, seemed to be offered in the statements of the above-mentioned authors. But a recent work by Armin Köhler,[3] proceeding from the laboratory of Alexander Schmidt and overthrowing his views on the formation of fibrin, again caused doubt.

According to Alexander Schmidt's investigations, the formation of fibrin takes place only when its generators, fibrinogen and fibrino-plastin, unite under the influence of a third body, fibrin-ferment. Thus these three bodies are necessary for the coagulation of the blood. These, however, are not all to be found in the circulating normal blood, at least not in sufficient quantity. It is true that the fibrinogen, which is produced from

[1] 'Experimentelle Beiträge z. Lehre v. d. Transfusion,' *Virchow's Archiv*, vol. lxii. p. 293 et seq.

[2] See his chief work, p. 91 et seq.

[3] *Ueber Thrombose und Transfusion, Eiter- und septische Infection und deren Beziehung zum Fibrinferment*, Dissertation, Dorpat, 1877.

the red blood-corpuscles, is always present in the plasma; but there is only very little or no fibrino-plastin, which is formed from the disintegrated white corpuscles immediately after the withdrawal of the blood. The ferment is not present in the blood which circulates within the vessels; this substance is also formed by the disintegration of the white blood-corpuscles.

But in defibrinated blood both fibrino-plastin and fibrin-ferment are to be found; if, therefore, defibrinated blood is introduced into the vascular system of a living animal, and if fibrinogen is supplied in sufficient quantity, there result more or less extensive coagulations, with their sequelæ.

But not every kind of defibrination yields the same results. The blood, which is obtained by means of pressure from the clots arising from spontaneous coagulation, acts most effectually when it is injected, where this is possible, at the temperature of the body. Longer contact with warm air destroys the ferment and makes the pressed-out blood inactive. The blood obtained by beating is much less capable of producing coagulation.

Köhler ascribes the extravasations observed by Magendie to the formation of coagula. It is precisely in the capillaries that the ferment will act most easily and energetically.

Köhler supports his opinion by a considerable number of experiments by himself. Only the smaller part of these deal with the application of blood, which has been defibrinated by beating, to the operation of transfusion. In the third part of his investigation he mentions ten experiments made on dogs where he transfused defibrinated blood of the same species. Before I begin a more particular discussion of these, I shall in a few lines sketch the picture drawn by Köhler to represent what he calls 'ferment poisoning,' a name he gives to the whole of the symptoms produced by coagulation in the living organism.

Soon after the beginning of the injection of blood containing ferment, such complete insensibility is observed that the eyelid, on the cornea being touched, closes slowly and hesitatingly; otherwise no form of stimulation provokes movement; the pupils are dilated. At the same time, or a little after, there occurs an attack of dyspnœa, lasting for a minute: while it continues, the action of the heart is strong and irregular. Lively borboryg-

mus, and evacuation of softened fæces. After about twenty minutes, the symptoms are past, and consciousness is restored. A further injection produces trifling symptoms; a certain degree of lassitude only is to be remarked. In the course of a few hours after the last injection, there is evacuation of blood-coloured stools, uneasiness, loud crying, evidently violent pain, considerable discharge of blood per anum, and the animal collapses in a short time. Death follows, while the temperature falls.

On *post-mortem* examination there are always found ecchymoses in the different organs, but varying in extent and distribution. Thus it is the lungs, in whose pulmonary arteries there is found more or less widely spread coagula, the endocardium, the large abdominal glands, the lymph glands, but especially the mucous membrane of the small and large intestines, and also that of the stomach, which present extravasations. The mesenteric glands are those which are most constantly affected. The blood coagulates imperfectly and with difficulty.

Starting from the supposition, that a separation of the fibrin takes place in the process, called by him 'ferment poisoning,' Köhler gives an interpretation of the individual symptoms. First, the narcosis which marks the commencement of the poisoning is explained. This is said to be caused by 'a certain temporary thickening, and on that account slow circulation, of blood in the brain.' Thus arterial anæmia is produced. It is not to be understood that actual coagulation took place in the brain, as it is only quite exceptionally that thrombi were seen in the cerebral vessels, and never greater or smaller apoplexies in this organ. Köhler ascribes the dyspnœa, which occurs almost at the same time, likewise to a temporary thickening of the blood. The dyspnœa occurred even 'when no extensive obstruction of the blood current by means of thrombi was afterwards observed.' 'Finally, the strong and irregular action of the heart points to hindrances in the whole circulation, which may of course be due to the above-mentioned cause.' The explanation of the whole process, then, is this: at first syrupy thickening of the whole blood, which is soon overcome by 'the reparatory processes of oxidation in the blood itself, as well as of the walls of the vessels.' It is only in the organs in

which peculiar conditions create a predisposition that the process begun goes on to actual coagulation. These 'peculiar conditions,' according to Köhler, consist in this: that in the capillaries of the organs chiefly affected 'peculiar and especially active changes in the blood, and particularly in the blood corpuscles, take place.'

If we abide by the facts of Köhler's experiments it must first of all be remarked that there is a striking inconstancy in the symptoms. The blood obtained by pressure, and containing abundance of ferment and fibrino-plastin, cannot once regularly produce thrombi when it is injected into an animal of the same species; even under the most favourable conditions—pressed blood from bullocks transfused into cats—when relatively large quantities are injected, the formation of thrombi may fail (as, for example, in the second series of experiments, Experiment 3). Moreover, in all these experiments, 18 altogether, there were only 12 positive, and 6 negative.

Now Köhler, indeed, attributes the extravasations of blood, in the organs where they occur, to formation of thrombi in the capillaries. If that were correct, one would no longer dare to speak of an inconstancy of the symptoms generally, but only of very considerable quantitative differences which remain unintelligible. But Köhler has adduced no proof that capillary apoplexies depend on thrombosis. He confines himself to the assertion, that the symptoms on the whole resemble those which may be produced by artificial capillary emboli, and that greater thrombi are found (though not constantly) elsewhere in the body, particularly in the arteries of the lungs, and, still further, that the lungs and intestines are attacked at the same time; and from these premises he draws his far-reaching conclusion. But *anatomical proof of multiple capillary thrombosis is wanting, and with it the sure foundation of the whole theory.*[1]

To this we may add that Ponfick,[2] 'not indeed regularly, but still by no means rarely,' saw precisely the same multiple extravasations even after direct transfusion from the artery of one animal into the vein of another of the same species—i.e.

[1] See also Cohnheim, *Allgemeine Pathologie*, vol. i. p 345 et seq.
[2] Loc. cit. p. 295.

under conditions which exclude Köhler's explanation, so that Ponfick could produce these or not at pleasure, according as he injected the defibrinated blood from the same species violently or gradually. By this it is at any rate proved that we are not compelled to assent to Köhler's conclusion.

So much for his theory on the whole. Let us now turn to the experiments in which transfusion of the defibrinated blood of dogs into dogs was practised.

Köhler remarks that dyspnœa, unconsciousness, borborygmus, &c., were present in a small degree, and sometimes were not present at all. Still among the ten cases notified, there were several with distinct signs of 'ferment poisoning,' and one that even ended fatally in a dog, after 25 + 25 + 30 c.cm. defibrinated blood of its own had been injected into it. On post-mortem examination, in this dog, in another severely ill, and in four others which suffered only from vomiting and diarrhœa, there were found, in a gradation corresponding to the severity of the disease during life, the 'typical' appearances; and there were even 'small thrombi in the arteries of the lungs' of the dog which died. 'In the four other dogs, it is true, every indication of it was wanting.'

Köhler insists that his peculiar way of going to work, differing from ordinary methods—by injection through the wall of an artery—has essentially contributed to give him clearer results than his predecessors have obtained.[1] By this proceeding, it is said, an intimate mixture of the 'ferment with the blood of the body,' considerably increasing the activity of the former, will take place. Beyond this he has no further ground which would satisfactorily explain the differences between the results of his experiments and those of his predecessors, among whom Mittler alone agrees with him in an exaggerated statement which is treated by Köhler himself with slight irony. Cohnheim[2] is certainly right when he is of opinion that 'all Köhler's ideas appear paradoxical in view of the innumerable transfusions of defibrinated blood which, especially in the last decades, have been made by very various experimenters on dogs and other animals, *without any recognisable injury to them.*' If the

[1] See especially the note, p. 33. [2] Loc. cit. p. 347.

objection made by Cohnheim himself, that small thrombi in the lungs and vessels of the body generally are comparatively harmless things, is of any value, well then we can readily take this harmlessness into account as regards the injection of defibrinated blood into human beings; there is no necessity that the golden tree of life should therefore wither for a long time to come. Nor does it wither; for what Köhler adduces from the literature of transfusion in support of his opinions is not calculated to satisfy an unbiassed reader. Thus he writes that [1] 'Schatz observed, soon after the transfusion of defibrinated blood, the formation of large thrombi, as also pneumonia resulting from an embolus.' Very good, but Schatz himself thinks that here the uterine veins were the seat of the thrombi formation.

I would, however, particularly remark that Panum [2] and Landois, in the two cases communicated in a previous extract in which they practised blood transfusions on animals, and both of which had a fatal termination, found no formation of thrombi in the lungs. Panum observes, 'The intestinal canal contained masses of mucus tinged with blood, and the mucous membrane was red and injected. The lungs were quite pale, without serous or sanguinolent infiltration, and all the other organs were normal.' Landois also relates nothing of the presence of 'typical' ferment poisoning. The small clots which he found in the right auricle, and here and there in the mesenteric veins, cannot vouch for ferment poisoning, as the autopsy did not take place until long after death.

Taking all into account, we may say, that the investigations of Köhler in themselves have brought under consideration new and very interesting views, which must be still further tested; and that the application of defibrinated blood in transfusion does not appear seriously endangered by them. So far as I know, the defibrinated blood obtained by pressure of a blood clot has not yet been much used, and this is even less likely to be so in future; neither is injection through the wall of an artery exactly necessary. This is all that can be said. It would be much to be regretted, should anyone allow himself to be so

[1] Loc. cit. p. 41.

[2] The description of what was met with at the autopsy is to be found in *Virchow's Archiv*, vol. lxiii; p. 50 of the reprint.

far misled as to refrain from the application of defibrinated blood, by conclusions apparently derived from uncertain premises, and to which a delusive support has been given by experiments. Here innumerable experiments and extended experience at the sick bed stand in opposition to inconstant individual results, which allure only through the shining veil of a plausible theory.

Köhler was still less able to bring forward proofs of his assertions from the literature of the subject. He mentions only four cases, and even these are not applicable in the sense in which he has taken them.

'Weickert and Simon Thomas could inject but little blood, on account of the coagulation which had already ensued;' assuredly, however, both made use of non-defibrinated blood: there can therefore be no question of 'ferment poisoning.' 'Roux saw suffocation suddenly take place; the heart and the left subclavian were found at the autopsy to be filled with clots.' This case occurred in the year 1830; twenty-five days after a gun-shot wound of the right shoulder, with shattering of the bones, there was profuse secondary hæmorrhage, which was repeated after a week had passed. Notwithstanding ligature of the subclavian the bleeding continued. In addition to all that is mentioned by Köhler, abscesses were found in the lungs. Although it is mentioned that 'the heart and the left subclavian were filled with clots,' this does not quite imply that these had been actually formed during the patient's lifetime; the abscesses found in the lungs betokened the existence of pyæmic conditions.

We come, then, finally to the case mentioned by Schatz, of which he himself says that the pulmonary emboli which were found came from the uterine veins. We are judging very charitably when we designate such kinds of proof as very slight and superficial.

The advocates of non-defibrinated—'entire'—blood have only one way of attaining the end desired by them, viz. through the addition of some substance which will act chemically and prevent coagulation in the freshly withdrawn blood. In such a proceeding it is of course necessary to be particularly careful that the substances employed to prevent coagulation

should not be of such a kind as to exercise an injurious influence on the red blood-corpuscles, or threaten their vitality. Experiments on this subject are not numerous.

Rautenberg[1] communicates the information, that an addition of carbonate of soda—12 centigrms. dissolved in 7·2 grms. of water, to 120 grms. of blood—is allowable in man and is sufficient. He himself designates this as a 'suggestion' (*Vorschlag*), and refers to experiments on dogs, which are not communicated at full length. In Panum's[2] works is found the notice, that Braxton Hicks, who, by the advice of Pavy, added phosphate of soda, had very unsatisfactory results in his six experiments on human beings. This is everything of the nature of serious suggestions. It is, however, not to be doubted that by systematic investigation we might at last find a mixture the addition of which would accomplish the end in view, but there hardly seems any actual necessity for beginning such a search. For on the basis of Köhler's experiments we shall add another to those causes which have hitherto existed for hesitation in making use of non-defibrinated blood for indirect transfusion. Panum, and those who agree with him, dreaded only from the transfused blood the formation of coagula and their consequences. Since Köhler has designated this form of blood as the direct conveyer of ferment and fibrinoplastin, there ought to be cause for constant anxiety lest the blood, while issuing in a half fluid state from the cannula, and being received in this condition into the circulation of the person into whom it is injected, bring on the very worst form of ferment poisoning.[3] How is this to be avoided? In comparison with this danger, that of poisoning by the use of defibrinated blood dwindles, in fact, into insignificance.

If non-defibrinated blood is to be transfused there is only a very short time at the operator's disposal, on account of the threatening coagulation; the transfusion must be made quickly, indeed almost impetuously (*stürmisch*), whenever any large

[1] 'Die Transfusion des Blutes,' *St. Petersburger med. Zeitschrift*, vol. xiii. p. 22, 1867.

[2] *Virchow's Archiv*, vol. lxiii. p. 35.

[3] *Vide* the writings of Köhler (loc. cit. p. 93), where indeed smaller clots are described as setting up 'ferment poisoning.'

quantities of blood are to be injected; and that is all the more dangerous with non-defibrinated blood. It is easy to understand why.

The red blood-corpuscles convey the oxygen. We wish by means of them to supply the organism with this gas. The blood to be injected must, therefore, either itself contain abundance of oxygen, or at least it must enter the body of the person into whom the blood is to be transfused in such a condition as will quickly permit the absorption of this gas. Another particular must be added. *If, within a short time, blood containing a large quantity of carbonic acid is transfused, then it may, on account of the presence of this gas, seriously endanger or even destroy life.*

Bischoff and Brown-Séquard [1] have already by their experiments firmly established the fact that large quantities of oxygen must be contained in the blood to be employed for restoring to life asphyxiated animals, since the blood stands in direct relation with the activity of the brain. Brown-Séquard succeeded in restoring a brain in which, by sudden interruption of the supply of blood to the organ, an entire loss of function was rapidly produced, and which after the lapse of about 3 minutes would have passed into death, by supplying it with blood rich in oxygen immediately before this space of time had elapsed. Black (venous) blood, containing little oxygen and much carbonic acid, has not this capability; the life-giving power of blood is in exact proportion to the amount of oxygen that it contains. Mixtures of blood and serum must, even if they are abundantly supplied with oxygen, contain at least 3 to 4 parts of blood to 10 parts of serum, in order to restore the lost activity.

Brown-Séquard found, moreover, that blood, which by absorption of carbonic acid had acquired a blackish colour, was even dangerous to life when to the extent of 0·2 per cent. of the body-weight it was somewhat too quickly injected. It was only by very slow transfusion, which made the elimination of the carbonic acid through the lungs of the animal possible, that he succeeded in preserving the life of the animal.

[1] See in Panum's principal work, loc. cit. p. 148 et seq.

These experiments were repeated with similar results by Eulenburg and Landois.[1]

Landois[2] afterwards added the important fact that red blood-corpuscles strongly charged with carbonic acid are very much more easily destroyed. The operation of reagents, which leave uninjured the blood that is saturated with other gases, is sufficient to produce in blood overcharged with carbonic acid complete disintegration with separation of the hæmoglobin from the stroma.

Defibrinated blood is rich in oxygen and poor in carbonic acid; non-defibrinated, venous blood—for arteriotomy is not as yet practised for the purpose of procuring blood—contains little oxygen, and so much carbonic acid that it can, by rapid injection, act poisonously. Panum, in his time, took particular notice of this circumstance, and certainly with perfect justice. Let us now come to the conclusion.

I consider, as entirely incontestable, the statement of Panum[3] 'that transfusion with defibrinated blood, as regards the safe and easy performance of the operation, deserves unconditional preference to transfusion with non-defibrinated, venous or arterial blood; that, in fact, transfusion of human blood into human beings could never be effected with safety, and would never attain essential importance, *if, on any other grounds, the use of defibrinated blood were inadmissible and if the desired aim could not be fully attained by it.*'

The vitality of the red blood-corpuscles contained in the defibrinated blood outside the body is dependent on conditions which are at least partially known.

First of all, the temperature is of decisive importance. This must never once go either above or below a definite and somewhat sharply prescribed limit, if the general vitality is to be preserved. The continuance of this vitality is also influenced by the state of the temperature. We are indebted to Landois for precise investigations of this influence.

It must be enforced as a universally important fact, that *sudden changes of temperature are to be avoided*, no matter

[1] *Die Transfusion des Blutes*, p. 8 et seq. Berlin, Hirschwald, 1866.
[2] Principal work, p. 163 et seq.
[3] *Virchow's Archiv*, vol. lxiii. p. 35.

whether the change is from a higher to a lower, or from a lower to a higher degree of heat. Slow cooling and slow heating are imperative.

Landois experimented in most instances with the blood of a rabbit; in doing so he made use of a physiological and of a chemical procedure. In the former the blood was withdrawn from the veins of the animal, defibrinated, then kept for twenty minutes in a water bath of a definite temperature, and when brought to the heat of the body it was again injected into the same animal. The chemical method of investigation consisted in heating the defibrinated blood for exactly the same time, and then observing whether a diffusion of the hæmoglobin into the serum or plasma took place. With regard to the rabbit, the following results were obtained.

Heat, which does not exceed 48° C. (118·40° F.), disturbs the function of the red blood-corpuscles but little on the whole; although when even a small quantity of the heated blood is injected into the circulation, there ensues an excretion of albumen through the kidneys. The red blood-corpuscles, when observed outside the body, do not exude hæmoglobin. If the temperature exceeds 48° C., then disturbances, ever becoming more important, show themselves by degrees, both in the characters of the red blood-corpuscles themselves and in the state of the organism into which the heated blood has been returned. A reddening of the serum is perceptible, corresponding to the degree of temperature used; the red blood-corpuscles begin to disintegrate, and at 58° C. (136·4° F.) the disintegration is complete. Most animals die. It is found, as a rule, on post-mortem examination that coagula have formed, and in Landois' opinion the fibrin of the stroma must be regarded as the nucleus of these.

Moreover, individual differences seem to occur. One animal died after the injection of 5 c.cm. of blood, which had been heated to 46° C. (114·80° F.) Another bore the injection of 21 c.cm. of blood, heated to 51° C. (123·8° F.) In both cases the body weight was almost the same—1,842 and 1,850 grms.

Landois also made experiments on the blood of other animals by the chemical method. The blood of lambs and of cattle was the most capable of resisting changes of temperature.

It is a well-known fact that blood frozen and then melted,

especially if these processes are repeated, shows a complete dissolution of its red corpuscles. On the other hand it may be cooled down almost to the freezing point without causing any perceptible impairment of their vitality. Panum has made this observation, which has received confirmation from Landois, Ponfick, Worm-Müller, and others.

The length of time, during which the blood remaining outside the vessels continues active, is essentially dependent on the state of the temperature. Landois states that a temperature varying a little above 0° C. (32° F.) presents the most favourable conditions for the preservation of its vitality. At the same time it must be particularly taken into account that the development of putrefactive ferments, and, generally, of organic germs, is prevented by such a low temperature. At all events it is necessary that, in collecting and preserving the blood, everything favourable to decomposition should, as far as possible, be avoided.

Landois induced Du Cornu, one of his pupils, to make more particular investigation of this matter.

Dog's blood remained from 5 to $5\frac{3}{4}$ days uninjured, when collected in a narrow-necked bottle, previously washed with boiling water, and containing small pebbles which had likewise been treated with boiling water, the bottle being closed with a well-fitting glass stopper, and the blood defibrinated without admission of air, and placed, surrounded with water, in the ice chamber. 'By being kept in a cool place' dog's blood, treated with less caution, was found in one experiment to remain fresh for 4 days.

Rabbit's blood is less capable of preservation. It may possibly be preserved for 72 hours, but even at 38 hours after its withdrawal from the body Landois saw decomposition set in.

Human blood—which, after having been defibrinated and filtered in the open air, was placed in ordinary bottles, so that these were, as far as possible, completely filled—was kept in an ice chamber for 14 hours, after a journey by carriage of about 4 hours in moderately warm air, and still retained its vitality (Author's observation).[1]

[1] Jürgensen, *Vier Fälle von Transfusion des Blutes*, p. 23. Berlin, Hirschwald, 1871.

The question has already been very thoroughly discussed *whether an increase of the quantity of blood within the vessels can take place without danger from plethora.*

An answer has been obtained by a special experimental investigation, and is as follows: Such over-fulness of the blood is not at all dangerous so long as the quantity injected is not such as to be quite out of the question in medical practice. In the previous section a minute account of the labours of Lesser and Worm-Müller has been given; I shall only remind the reader here that an increase of blood to the extent of four-fifths of the normal amount can be borne without injury to the health of the individual into whom it is injected.

I should like to enter more thoroughly into a communication of Ponfick [1] which may be of far-reaching importance.

He found that a mixture which is known to have no injurious action on the red blood-corpuscles—viz. artificial serum, consisting of a 1 per cent. solution of chloride of sodium, and egg albumen—can be injected into the normally filled vessels in large quantities without causing any disturbance worth mentioning. This mixture, to the amount of about half the quantity of blood present, was injected without previous withdrawal of blood. The symptoms in the animal consisted of moderate oppression, somewhat more frequent respiration, accompanied by more ample movements of the chest and a certain increase of the activity of the abdominal respiration. All this continued but a short time. There invariably followed abundant evacuation of fæces, mostly fluid, consisting of mucous, more rarely watery, slightly bile-coloured material, the whole amounting to not more than 0·1 per cent. of the body weight. The urinary secretion was peculiar. Within the first 24 hours after the transfusion the urine did not increase at all, or at least but little; the specific gravity sank considerably—from 1,045–1,060 for that passed by night, and from 1,030–1,040 for that passed by day, to 1,010–1,025. A large quantity of the injected albumen appeared in the urine, the reaction of which was at the same time alkaline. After two days at most, the albumen entirely disappeared from the urine, and the normal condition generally was restored.

[1] Loc. cit. p. 275 et seq.

The experiments of Cohnheim and Lichtheim [1] also testify to an enormous tolerance of the system. A 0·6 per cent. solution of sodium chloride could, to the extent of three times the amount of the normal quantity of the blood, be injected into dogs without causing death. The difference here between their experiments and those of Ponfick consists only in this, that a considerably increased activity of the renal and salivary glands, and at the same time increased intestinal secretion, were present.

If the experiments of Kronecker [2] and Sander, as yet made known only in a short communication, afford constant results, those just mentioned receive additional importance. A solution of 6 grammes of chloride of sodium and 5 grammes of caustic soda in a litre of water was sufficient to preserve the life of dogs that had been bled, into the veins of which it had been injected in quantities corresponding to the amount of blood which they had lost.

The whole sum of our experience compels us to come to the conclusion that, *in the quantities of blood which are transfused for therapeutic ends, an over-filling of the vascular system is not to be feared; that therefore, so long as it is not required on other grounds, a stand ought to be made against a withdrawal of blood preceding or accompanying transfusion.*

Even Panum,[3] formerly the decided champion of 'depletory' transfusion, recognises latterly the justice of the conclusions drawn from the experiments of Lesser and Worm-Müller.

The investigations of possible *changes* in the *metabolism* of the body after the transfusion of blood from an animal of the same species may be discussed without considering whether or not the transfusion was preceded by a withdrawal of blood.

Panum was the first to demonstrate that the metabolism of an animal, which receives blood from one of its own species to replace part of its own blood, remains unchanged; he has also particularly shown that the removal of the fibrin from the injected blood has no influence.

[1] *Virchow's Archiv*, vol. lxix., and Cohnheim's *Allgemeine Pathologie*, vol. i. p. 366 et seq.

[2] *Berliner klin. Wochenschrift*, 1879, p. 767 (No. 52).

[3] *Virchow's Archiv*, vol. lxiii. p. 52.

I again give a summary of his first experiment.[1]

A dog, of 6,800 grms. weight, with empty intestines.

Blood-withdrawal of 100 c.cm. Transfusion of 64 grms. of defibrinated blood from another dog. Therefore an actual withdrawal of 36 grms. = 0·5 per cent. of body weight.

The dog had previously fasted completely for a little more than two days.

The urine excreted during the last 24 hours before transfusion amounted to 75 c.cm., of specific gravity 1,055, containing 7·5 grms. of urea.

After transfusion the dog was again made to fast. It passed, in the two days succeeding the transfusion, 148 c.cm. urine, of 1,055 specific gravity, and containing 14,652 grms. of urea; thus, in 24 hours, 74 c.cm., and 7,326 grms. The loss in weight by insensible perspiration amounted in the 24 hours before transfusion to 130 grms., after it to 141 grms.

Thus there was scarcely any apparent change; at least the total quantities remained the same.

Even the growth of a young dog was not checked by repeated withdrawals of blood followed by transfusion of defibrinated blood. Panum gives a convincing experiment to prove this.[2]

From a well-bred dog, operated on whilst a pup, there was—

	I. June 9.	II. June 10.
Withdrawn . . .	200 c.cm.	160 c.cm.
Transfused . . .	128 ,,	152 ,,

The absolute loss thus amounted to $72+8=80$ c.cm.

The dog in a fasting condition—just before abundant feeding with a mixed diet—weighed:—

June 8.	9,020 grms.	(weight with which comparison is made).	
,, 11.	10,520 ,,	+ 1,500 grms.	
,, 15.	10,700 ,,	+ 1,680 ,,	
,, 30.	12,430 ,,	+ 3,410 ,,	

On June 30, by withdrawing blood and partially replacing it by transfusing the defibrinated blood of another dog four times in succession—the quantity transfused being about 54 per cent. of the blood withdrawn—an absolute loss of 107 grms. took place.

[1] Principal work, p. 158 et seq. [2] Experiments 6 and 7, p. 164 et seq.

The body weight, under the same conditions as those formerly specified, and compared with that of June 8, amounted to:—

July 2.	12,760 grms.	+ 3,740 grms.
„ 3.	13,120 „	+ 4,100 „
„ 15.	15,640 „	+ 6,620 „

Thus within the space of 37 days—in which, in addition to those of the operation, there was also one day and a half in which food was entirely withheld—an increase to the extent of nearly three-fourths of the original weight had taken place in a growing dog.

Worm-Müller,[1] Tschiriew,[2] and Forster [3] have made investigations in order to ascertain how it is that, after transfusion of defibrinated blood into fasting dogs, the renal secretion exceeds the normal quantity. Landois [4] arrived at almost the same results.

The discussion of the whole of this question is not appropriate here, and would lead us too far. I therefore confine myself to those experiments which, as they were made with smaller quantities of blood—about one-third of the normal quantity—are best adapted for application at the sick bed.

In fasting dogs, after the injection of defibrinated blood amounting to one-fourth or one-third of the normal quantity of the whole blood, and without any previous depletion having been practised, an increase of urinary secretion is produced, which, especially in the time immediately following transfusion, is very considerable, but which also continues for several days.

The quantity of urea is also increased on the whole to an extent corresponding to the increase of the urine, and according to the time that has elapsed.

The following table gives a summary of the numerical values:—

[1] *Transfusion und Plethora.* Christiania (University syllabus), 1875.

[2] 'Der tägliche Umsatz der verfütterten und der transfundirten Eiweissstoffe,' *aus dem physiologischen Institute zu Leipzig. Verhandlungen der Königl. Sächs. Gesellschaft der Wissenschaften zu Leipzig*, Mathematical and Physical Class, vol. xxvi. p. 441 et seq. 1874.

[3] 'Contributions to the Theory of the Decomposition of Albumen in the Bodies of Animals,' *Zeitschrift für Biologie*, vol. xi. p. 406 et seq. 1875.

[4] Loc. cit. p. 38 et seq.

Number of the Experiment	Amount of Blood Transfused over the Normal Amount, as per Cent. of the Blood normally present	Amount of Urine on the Day before the Transfusion	Amount of Urine on the Day following the Transfusion	Average Amount of Urine on the Days preceding the Transfusion *A*	Average Amount of Urine on the Days following the Transfusion *B*	*A*=100 *B*=	Amount of Urea on the Day before the Transfusion	Amount of Urea on the Day after the Transfusion	Average Amount of Urea on the Days preceding the Transfusion *C*	Average Amount of Urea on the Days following the Transfusion *D*	*C*=100 *D*=
		C.cm.	C.cm.	C.cm.	C.cm.		Grms.	Grms.	Grms.	Grms.	
Worm Müller I. (loc. cit. p. 16)	about 28	36	90	39	59	151	3·024	6·865	3·12	4·69	150
Worm Müller II. (p. 22)	„ 30	105	247	102	153	150	5·99	7·04	7·13	7·81	110
orster I. (loc. cit. p. 508)	„ 25	162	374	158	266	168	11·6	15·2	13·0	15·6	128
Forster II. (ibid.)	„ 25	542	1,580[1]	671	835	124	14·1	17·5	15·0	16·8	112

[1] The dog, as the result of an oversight, received almost double the amount of water that he got previously or afterwards.

The fact, that inconsiderable variations exist in the individual experiments with regard to absolute quantities, ought, most naturally, to be ascribed to individual diversities, especially to the state of nutrition, age, &c. Such variations are, of course, found in all experiments on tissue metamorphosis.

Worm-Müller has, in his experiments, closely observed the *condition of the blood*, employing simultaneously various methods—enumeration of the red blood-corpuscles, comparison of colour according to Welcker's method, chemical analysis—and he arrives finally at the following opinions :—

1st. The increase in the quantity of the blood is transitory. If an increase amounting only to about 30 per cent. of the original quantity is produced, then in the course of the day immediately following the operation the quantity of blood contained in the vascular system appears to have fallen to the original amount.

2nd. The plasma of the transfused blood supplies material for the increased formation and excretion of urea during the first few days.

3rd. The blood corpuscles remain from about 2 to 4 days unchanged, and do not break up, even when they are present in the blood to an extent far exceeding the normal quantity. Their subsequent disintegration is extremely slow, and the process never goes so far as to the elimination of albumen, blood, or bile pigments by the kidneys.

For confirmation of this, reference may be made to the original paper. It is, however, worthy of mention that animals injected with not too large quantities of blood from one of their own species continue for months in permanently good health. Immediately after the operation, and after moderate overfilling, even increased comfort and energy are manifest. Thus Worm-Müller saw a rabbit, into which had been transfused 27·6 per cent. additional blood, copulate a few minutes after the completion of the operation. If there had been previous depletion of blood, these effects appeared still more distinctly.

It was only an increase of more than 100 per cent. that brought on disturbances—lassitude, want of appetite, and oppression (Worm-Müller, Lesser, Panum).

The *condition of the bodily temperature* after transfusion of blood of the same species must be discussed by itself.

First of all, it stands as a firmly established fact, *that the temperature does not necessarily rise after the transfusion of blood from an animal of the same species; it has, however, been ascertained that it* MAY *rise.*

Liebrecht [1] communicates experiments on dogs which prove this. The blood, in nine dogs, was transfused directly from the crural artery into the crural vein of the same animal: in five cases no increase of temperature took place; but in four cases the temperature rose so much that in one it reached 42° C. (108° F.) It is specially worthy of remark that two of the dogs thus affected with fever had borne previous transfusion without showing any increase in temperature.

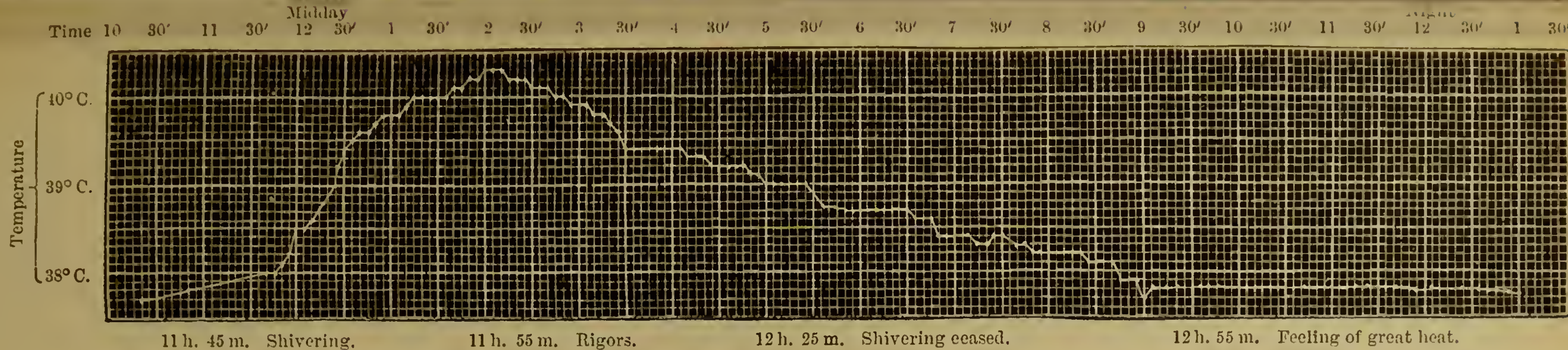
The same thing is true of human beings. Out of 6 cases which came under my own observation, and in which the condition of the bodily temperature was closely watched, there were two in which certainly no increase appeared. As, however, in all these there were serious pathological conditions present, they are, of course, less convincing than experiments on animals made with the simplest arrangement of conditions. However, there appears in man to be no absolute necessity for any increase of temperature. If such a state of matters does exist, there is also usually a greater or less feeling of cold, amounting, it may be, to rigors.

The course of the temperature, so far as I know, has, in its minutiæ, not been quite closely followed. I give particulars, therefore, of a case from my clinic to which special attention was paid.

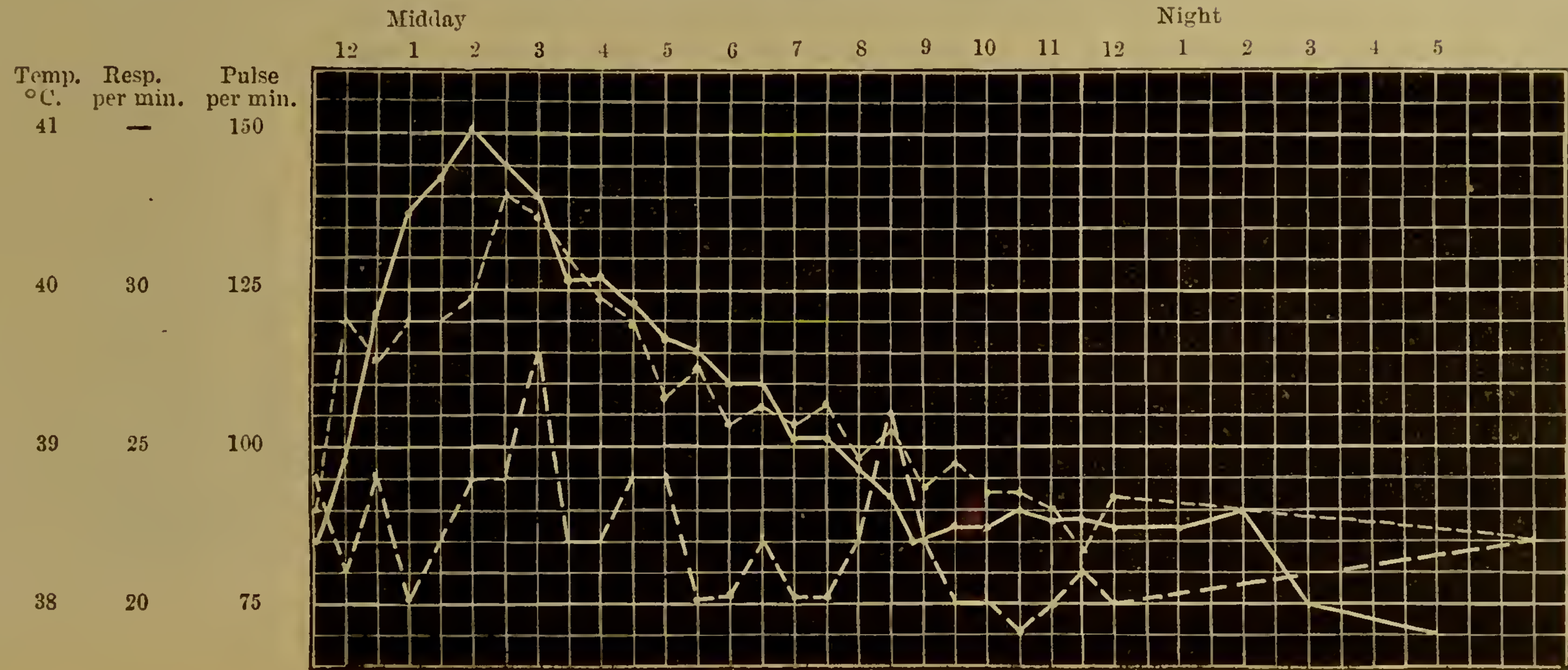
A woman, 34 years old, otherwise perfectly healthy, had suffered from an unusually severe hæmorrhage from a perforating gastric ulcer. Ten days after the hæmorrhage had ceased there was found (calculated by Hüfner's method [2]) a quantity of hæmoglobin, amounting to 6·72 per cent.; whilst the clinical symptoms showed a very high degree of anæmia to be present.

[1] *Centralblatt für die med. Wissenschaften*, 1874, pp. 580, 581.

[2] See Carl v. Noorden, 'Contributions to Quantitative Spectrum Analysis, especially to that of the Blood,' from the Laboratory of Professor Hüfner, *Zeitschrift für physiolog. Chemie*, vol. iv.



Curve II. showing Temperature, Respirations, and Pulse.



In the space of 39 minutes, by means of Landois's burette-transfuser, 270 c.cm. of blood were transfused into a vein of the arm, without causing the smallest impairment of the general health. The blood had been previously withdrawn by venesection from a robust vine-dresser, carefully defibrinated, filtered, and brought almost to the temperature of the body. The thermometer employed for the measurements had been previously compared by Professor von Reusch with the standard instrument here. It was about 6 to 7 tenths of a degree too high. In order to simplify matters I deducted generally 0·7° C. Previously the patient's bodily temperature, during 7 days' observation, had never, in the evening, exceeded 37·7° C. (100° F.) All the measurements were made in the rectum by my assistant physicians ; the thermometer was read off every five minutes. The pulse and respiration curve are here likewise communicated. (See charts on previous page.)

During the transfusion the bodily temperature rose very gradually; then followed a tolerably quick rise, and the maximum was reached $3\frac{3}{4}$ hours after the operation was completed; 10 hours 15 minutes afterwards the normal temperature was restored. The thermometer went as high as 40·3° C. (104·5° F.)

We now turn our attention to what takes place *when transfusion of the blood of* ANOTHER SPECIES OF ANIMAL *is performed.*

The main question here is, whether the blood-corpuscles of one species of animal, transfused into the circulation of one of another species, permanently retain their vitality and activity.

Panum has already answered this question in the negative, supporting his opinion partly by reference to the facts specified in earlier literature and partly by the results of his own experiments. The labours of Landois, Ponfick, and Worm-Müller have supplied full confirmation of Panum's statements, and, by going into details more thoroughly, they have furnished very valuable additions.

In order to give a picture of the symptoms which appear after transfusion of blood of a different species, I shall now relate the essential particulars of Panum's second experiment.[1]

From a dog, weighing about 7 kilos., blood to the extent of

[1] Principal work, pp. 204, 205.

480 c.cm. was withdrawn from the carotid, after which all signs of life disappeared. The corneal and conjunctival reflexes and the respiration were suspended. Then 320 c.cm. of lamb's blood, freshly withdrawn, defibrinated, and still warm, were gradually injected into the jugular vein. Each injection amounted to 32 c.cm., and, after the second, crampy contractions of the diaphragm came on; after the third, the respirations were regular; after the fourth, the eyes were again sensible to touch, voluntary motion and sensation gradually returned; the latter appeared even to exceed the normal degree. After the operation was completed, the dog barked without any apparent cause, looked wild, moved his head and neck powerfully, but was so feeble as to be unable to stand on his legs. Soon afterwards an extremely violent hæmorrhage took place from the small vessels in the wound that had been made, which did not cease until more than an hour had elapsed. The aqueous humour of both eyes was strongly blood-stained; the temperature had risen in a striking way. Respiration and pulse became strong; the latter was somewhat accelerated. Two hours after the operation, the excitement, barking, and wild appearance ceased, the strength decreased more and more, the pulse became feeble; and in three hours and a half after the operation death ensued.

The blood transfused was equivalent to somewhat more than half of the dog's own blood.

I shall now follow this up with a description of the symptoms accompanying direct transfusion from the carotid of a lamb into the cephalic vein of a phthisical woman, as I have myself observed them.

This is the first and only case in which I have practised transfusion of lamb's blood; it took place in May 1874, and is more particularly described in the dissertation of Dr. Haueisen.[1]

About 10 cm. of the carotid was exposed; into this a fine cannula was inserted and ligatured, through which the blood passed from the lamb into the vein of the woman. The transfusion lasted for about 1½ minute. Soon after the beginning of the operation dyspnœa came on, which increased rapidly and

[1] *Ein Fall von Lammbluttransfusion auf den Menschen.* Tübingen, 1877.

was combined with a considerable amount of restlessness ; the pupils became dilated. On various parts, particularly on the outer surface of the forearm, and on the face, considerable dilatation of the capillaries was seen, so much so that they looked like a branching, brownish red network. The transfusion was commenced at 31 minutes past 4, and occupied $1\frac{1}{2}$ minutes. The following symptoms were observed after the transfusion :—

May 21.

4.35. Still considerable dyspnœa.

4.45. Respiration calmer, capillary dilatation less, pupils no longer dilated.

5.10. Feeling of cold, particularly in the feet.

5.20. Slight rigor.

5.39. Moderately strong clonic contraction of various groups of muscles.

6.4. Respiration quiet and regular.

6.20. Very fluid and not very abundant stool; feeling of intense thirst.

6.45. Feeling of constriction; capillary dilatation has disappeared.

7.0. Skin of the face somewhat moist.

7.30. Rather more perspiration on the forehead.

10.30. Irregular pulse.

11.30. Frequent respirations for a few minutes.

May 22.

12.42 (A.M.). Liquid bloody stool ; great thirst.

$\left.\begin{array}{l}1.0\\1.30\end{array}\right\}$ Feeble, intermittent pulse.

2.0. More perspiration.

$\left.\begin{array}{l}2.20\\2.50\end{array}\right\}$ Small quantity of liquid, bloody stool.

3.50. Sleep.

4.55. Bilious vomiting; soon after, icteric colouring of the conjunctiva and of the skin of the face.

5.45. Liquid stool, with very little blood.

6.0. More distinct icterus, spreading over all the skin of the

body, the mucous membranes pale, the pulse small and irregular.

6.30. Desire to go to stool, without defæcation; abdominal pains.

7.30. Vomiting of a small quantity of bile-coloured material.

7.50. Moderately abundant stool, with traces of coagulated blood.

9.30. Small stool, without blood, but mixed with a little urine.

11.0. Yellowish pulpy fæces, without blood.

12.15. Frequent desire to go to stool, with abdominal pain.

2.30. Liquid stool, without blood; urine dark.

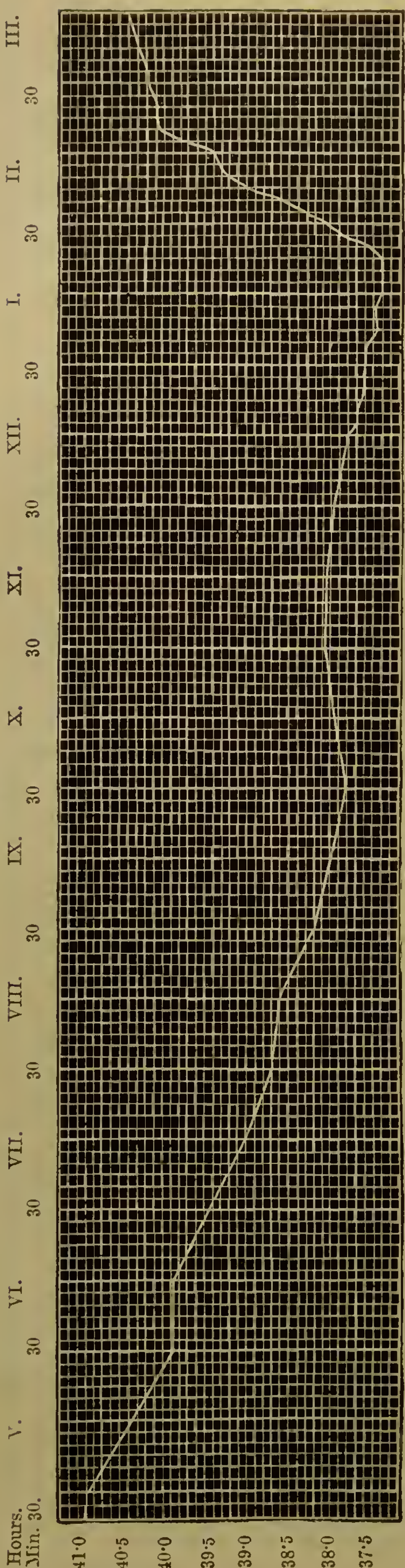
7.0. Icteric colouring considerably less. As sleep is broken by the constantly recurring desire to go to stool, 2 cgrms. of extract of opium were given in the form of a suppository.

In the further course of the experiment it is specially to be remarked that during the period extending from the 22nd to the 43rd hour after the operation the patient secreted no urine, the bladder being entirely empty. In the urine passed during the 22 hours immediately succeeding the operation, the quantity of the colouring matter of the urine was $7\frac{1}{2}$ times greater than in the normal concentrated urine of the morning; in that which was passed after 43 hours it was still $3\frac{1}{2}$ times greater, as estimated by Von Vierordt according to his method of spectral analysis. Blood and bile pigments were not present in the urine, nor, indeed, were there any traces of them.

The urine passed at 1 h. 49 m. after the operation, which was not applicable for other investigations on account of its contamination with fæces, contained no albumen. This was only found in what was passed 22 hours after transfusion, and it appeared most abundantly in the urine passed $52\frac{1}{2}$ hours after: somewhat more than four days later it had entirely disappeared.

On the ninth day, there appeared a widespread urticaria—a result very often observed even at so late a period after the transfusion of lamb's blood—which continued for several days, with the usual uncomfortable symptoms.

The following cut gives a graphic representation of the



Curve III.

course of the temperature. It is to be remarked that, during the last three weeks before the operation, the patient's temperature on the average had been—

7 A.M.	1 NOON.	7 P.M.
37·3° C.	38·3° C.	39·3° C.

During the latter part of this period the average was not quite reached (see Curve III.)

All observations place it beyond a doubt that *there exists a very distinct difference in the symptoms which show themselves after transfusion of blood from animals of a similar and from those of a dissimilar species.*

The cause of that difference may be thus briefly indicated:—

The red blood-corpuscles from an animal of a similar species do not disintegrate after transfusion, while those from an animal of another species do.

Moreover, the blood corpuscles of the individual who is the subject of transfusion may be endangered by the serum contained in the injected blood, and may even undergo partial solution. The destruction of the red blood-corpuscles gives rise to the disturbances which appear after the transfusion of blood from another species of animal.

It will be sufficient to mention the principal conclusions arrived at from the numerous experiments. And it may be taken for granted that it is perfectly permissible to apply to human beings the essential results of the experiments made on animals.

It is first of all to be observed that *the blood corpuscles of one animal do not remain uninjured in the serum of another*. They disintegrate, and their hæmoglobin separates from the stroma after many and various physical changes have taken place in them (Creite,[1] Landois, Ponfick).

The blood of one species of animal is very varied in its action towards that of another species. The serum and the red blood-corpuscles must be considered separately in this connection.

Thus, the serum of dog's blood dissolves the blood corpuscles of all other species of animals extremely quickly; the corpuscles of the cat alone form an exception, standing as it does in nearer relation to the dog in the natural order of animals. The blood corpuscles of the dog show themselves, on the contrary, to be very capable of resistance to the blood of any other species.

The temperature at which solution takes place has great influence on the rapidity of disintegration; at the temperature of the body the blood of another species is decomposed much more quickly than at the temperature of a moderately warm room.

Landois gives the following table with regard to dog's serum:—

Blood from—	Rabbit.	Sheep.	Guinea Pig.	Man.	Cat.
			Temperature, 20° C.		
Perfect solution after minutes .	15	17	15	56	Only a few blood corpuscles dissolved.
			Temperature, 47° C.		
Perfect solution after minutes .	2·5	1	1	9	Ditto.

[1] 'Experiments on the Action of Serum-Albumen when injected into the Blood,' *Zeitschrift für rationelle Medicin*, vol. xxxvi. p. 90 et seq., 1869.

The blood corpuscles of the dog, on the contrary, in all kinds of serum, in a moderately warm room, continue entire at least for days, or are only changed to a small extent.

We have still to mention the action of human and lamb's blood on each other.

In lamb serum, human blood corpuscles begin to dissolve, in a moderately warm room, not until after 7 hours, and even after 22 hours they have not yet undergone entire solution.

In human serum the blood-corpuscles of the lamb quickly undergo solution. With a small addition of corpuscles, a lac-colour appears in 3 to 6 minutes; with a larger addition, it shows itself immediately.[1]

All these statements are taken from Landois, whose manner of investigating was, to put 4 or 5 c.cm. of perfectly clear serum into a test glass, and to add so much defibrinated blood that the mixture became perfectly opaque. The dissolution of the red blood-corpuscles betrays itself at first by a translucency in the hitherto muddy and opaque fluid; it is ended whenever the whole has become quite clear and transparent.

The observation of what happens to blood of a different species, when injected into the circulation, agrees well with what may easily be noticed when the blood is outside the body. The dissolution of the foreign blood may be observed either with the help of the microscope, or by means of Landois' 'sulphate of soda test,' which has been already described, and, when

[1] The different statements in the memoir of Fiedler and Birch-Hirschfeld deserve to be compared with the above. According to these investigators, lamb's blood corpuscles do not undergo solution in human serum; there was only observed in them a slight swelling and paleness. This appeared after the lamb's blood corpuscles had lain for some hours in human serum, and was observed to remain unchanged during four to five days.

Human blood corpuscles in the serum of lamb's blood show, some hours after, a more distinct contour; the surface becomes slightly rugous, the margin in many cases somewhat serrated. At the same time the colour of the corpuscles becomes deeper. It may be mentioned still further that human blood corpuscles in the serum of sheep become irregularly grouped together in large or small heaps. *A solution of human blood corpuscles in the serum of sheep could not even be confirmed after daily observation for four or five days* (*Deutsch. Archiv für klin. Medicin*, vol. xiii. 1874, pp. 590, 591).

More precise statements on the external conditions under which this experiment was made are wanting; the contradiction is perhaps only an apparent one.

larger quantities have been injected, by examination of the urine. Finally, Worm-Müller has also undertaken the direct enumeration of the blood corpuscles. Before entering further on this subject, I shall communicate the result of what takes place during the process of dissolution, as observed directly under the microscope.

Creite has already remarked that the blood corpuscles of one species introduced into the serum of another species aggregate into balls, and form unshapely masses, in which the individual corpuscles are no longer distinguishable; whilst a similar effect is not produced by the addition of serum from blood of the same species. Landois [1] describes these processes more precisely:—

'After the blood corpuscles are mixed with the serum of a different species they exhibit in many cases, first, a change of shape, shrinking to mulberry-like forms, and not seldom displaying a lively molecular movement. As an example, I may mention the blood of a guinea pig mixed with the serum of a dog. Many kinds of blood, however, do not exhibit this mulberry appearance; but another change of form may be at once distinguished, akin in some respects to the mulberry appearance; the cells swell out with small globular projections, which for the most part become drawn out at the same time into fine points, so that the figure resembles a star or a stramonium capsule. As the substance of the formerly disc-like corpuscles must thus be distributed over the globular form, the cells are all apparently diminished in size. When thus changed in form the blood corpuscles are peculiarly apt *to aggregate into larger or smaller groups.* This aggregation takes place most easily when the cells are closely congregated together in the serum. These groups are often seen with the naked eye as large red masses swimming about in the serum, and then rapidly sinking to the bottom. This phenomenon is caused by a softening of the margin of the blood corpuscles, whereby, at the same time, their substance becomes very glutinous. Under the microscope the cells are seen placed very close to each other; the cells cannot be separated from one another by pressing on

[1] See his principal work, p. 159 et seq.

the cover-glass. They become elongated, often appearing as if held together by fibres of the substance of the blood corpuscles; when the pressure is removed the mass again contracts. The softening of the margin is also discernible by this, that by pressure on the cover-glass the blood pigment can often be pressed out of the corpuscles. The agglutination of these aggregated cells plays an important part in the transfusion of blood of a different species. It is self-evident that, when such masses are present in the circulation of the animal operated on, there must ensue extensive obstruction of small vessels; globular emboli (Hueter) are formed, combined of course with symptoms of stagnation in the areas of vessels lying on the remote side of the embolus.

'The further change, which is manifested in the cells which have now become globular, is gradual decolorisation, the hæmoglobin separating from the stroma. The blood corpuscles become by degrees paler and paler, until at last the totally decolorised stroma remains behind.'

From the masses of stroma, now bereft of its hæmoglobin, there then arises a fibrin-like substance—the 'stroma-fibrin.' Its formation can be closely followed under the microscope: 'After the hæmoglobin has been set free from the blood corpuscles, the contour of each individual cell in the agglutinated masses can still be at first distinguished; but, as soon as a current in the surrounding fluid ensues, the mass of stroma is agitated hither and thither, by which means the agglutinated stromas, lying close together, become elongated to soft, delicate filaments, and at the same time the contour of the cells disappears. Thus the formation of the fibrous masses from the disintegrated mother-cells can be followed step by step.'

It requires no proof that this stroma-fibrin may, on its part, both directly and indirectly, become a cause of obstruction in the vessels, as Landois has further shown.[1]

Another fact comes to be considered. Large quantities of hæmoglobin introduced into the circulation cause coagulation. Naunyn was the first to discover this. Landois observed, justly, as it appears to me, that this purely chemical phenomenon will equally occur whether the hæmoglobin, set free from its union

[1] Loc. cit. p. 249.

with the stroma, has had its origin within the vessels, or whether solutions of hæmoglobin have been injected into them. In the one case, a more solid formation of coagula may occur in the vessels directly concerned—more concentrated solutions then come together—in the other case, there exists a smaller degree of concentration, corresponding to a looser coagulation with less blocking in particular parts. Perhaps, however, this smaller degree of coagulation may be of greater importance when the amount of the whole is looked at. Köhler considers the presence of dissolved hæmoglobin in the blood as a doubtful occurrence; he thinks that a rapid development of ferment takes place, and the hæmoglobin set free from the stroma accelerates by contact the union of the substances which give rise to the coagulation.

We may now pass to the important question, What *anatomical changes* are found in the body of an animal into which the blood of another species has been transfused?

There exist the precise investigations of Landois and Ponfick; the fundamental features have already been established by Mittler, and also by Panum, who has, moreover, brought the earlier literature to bear fully on the decision of this question.

It must first be assumed that, in general, an escape of hæmoglobin, set free from its combination with the stroma, or still combined with it, and therefore an escape of red blood corpuscles, has taken place. All the organs of the body may be thereby affected—some in a high degree.[1]

The kidneys are severely affected; this may be considered as certain. Panum found an almost complete absence of urea in the urine of a dog into which lamb's blood was injected; the functional insufficiency of the kidneys after transfusion of blood from another species of animal was thus made manifest.

Ponfick[2] gives the following minute description of the anatomical state of the kidneys:—

[1] This is a summary of the 'typical' appearances observed by Köhler, who, indeed, does not make a marked distinction between the effects of the transfusion of blood from similar and dissimilar species of animals, but regards ferment poisoning as the common cause. The previously-mentioned interpretations by Köhler of the individual symptoms of his 'ferment poisoning' are thus applicable here.

[2] Loc. cit. p. 306 et seq.

'In cases which terminate in death, as well as in those less severe cases in which a fatal termination is anticipated by killing the animal, both kidneys are found to be much swollen, but by no means always congested; on the contrary, especially at the cortex, they frequently appear strikingly pale, and of a dirty greyish-brown colour. The capsule is easily stripped off; on the tightly distended and quite smooth surface are to be seen scattered over the peculiar brownish ground-substance numerous sharply defined spots and streaks of red-brown or dark coffee-brown colour. In their appearance, as well as in their distribution, they quite remind one of the well-known multiple spots in nephritis hæmorrhagica. On section they are seen in great numbers in the cortex, but less sharply defined from the surrounding parenchyma, which is much swollen, rather pale, and of a uniform colour throughout. The pyramids of Ferrein, like broad grey yellow lines, give to the interior a coarsely striated appearance. The Malpighian bodies are little prominent, on account of their not containing much blood. With regard to the medullary pyramids, they are large and much congested at the periphery; on closer inspection one can distinguish brown and red stripes passing towards the papilla and alternating with great regularity with one another. In the most severe cases, the brown lines may so predominate that the intervening reddish lines can with difficulty be distinguished. By pressure on the papilla there issues forth a fluid—sometimes blackish brown, sometimes clear—in which extremely small bodies are seen distinctly in suspension. A similar fluid fills, in varying quantities, the pelvis of the kidneys and the urinary bladder. The cases which almost immediately terminate fatally are characterised by complete emptiness of these portions of the urinary system. The fatty tissue of the hilus is frequently œdematous to a striking extent.

'A microscopic examination of the kidneys shows that all the brown spots and streaks in the cortex, and the radiating lines in the medulla, are caused by one and the same change, viz. *the presence of solid plugs in the lumen of the convoluted as well as of the straight tubules.* The colour of this cylindrical plug in the first few days is absolutely like that of the red blood-corpuscles; it is only in the later stages that it assumes

a darker, more brownish shade. *But at no time does it actually depend on the presence of coloured cells within the tubuli, but on a uniform imbibition of a kind of hæmoglobin by a ground-substance, which is either hyaline or granular.*'

Landois adds that fatty degeneration of the epithelium of the urinary tubules frequently occurs; he has also observed hæmoglobin crystals in the convoluted urinary tubules.

The digestive tract also is often the seat of considerable anatomical changes. These betray themselves during life by peristaltic movements, which are frequently very violent, and which cause a discharge of blood corpuscles or separated hæmoglobin with the contents of the intestines. Ponfick gives the following description:—

'The inner surface of the stomach is seen to be covered with viscid mucus, sometimes tinged coffee-brown by the admixture of blood, but the mucosa is comparatively little swollen and reddened; only at times did I notice isolated hæmorrhagic infarcti on the crests of the folds, perhaps the result of violent emetic movements. The duodenum and the whole of the ileum contain a greater or less abundance of reddish-grey semi-fluid masses, at one time of a more viscid character (by epithelial desquamation), at another time of a more serous character. It is remarkable that these masses do not by any means contain a quantity of red blood-corpuscles corresponding to their redness, but nevertheless they contain very considerable quantities of hæmoglobin, as is proved by spectroscopic examination. The mucous membrane is dark red and much swollen; the villi unshapely, large, and broad; thus rendering the surface peculiarly coarse and uneven. This redness and swelling extend in varying intensity over the whole of the colon, being most marked in the sigmoid flexure; the rectum is usually less powerfully affected. Whilst the dark purple colour of the remainder of the intestinal mucous membrane, as is proved by microscopic examination, is produced only by the highest degree of general congestion of the vessels, there are found in the flexure also real hæmorrhages into the tissues, and, indeed, constantly on the summits of the longitudinal folds.'

Landois adduces no statements which essentially differ from this report.

All the other parts of the body are affected in a smaller degree, and much more rarely.

What we have therefore to deal with is exudations, mostly of such a kind as contain separated hæmoglobin, rather than red blood-corpuscles, in the tissues or on free surfaces. Thus, there are to be found blood-coloured areas of small extent in nearly all the organs, and effusions into the peritoneal and the pleural sacs ; even the cerebro-spinal fluid was seen by Panum to be blood-coloured. It is an important observation of Ponfick's that the urine, coloured red by free hæmoglobin, had after 20 hours, at longest, again become colourless. It may be concluded from this that, under favourable external conditions, the organs injured by transudations saturated with hæmoglobin may again soon be relieved of their burden. It remains to be mentioned that Landois observed fatty degeneration of the cells of the liver. We may add the results of the direct counting of the blood corpuscles by Worm-Müller.

'By counting the blood corpuscles, and checking this by the help of colorimetric estimations, analysis of the blood, and microscopic examination, we have directly proved that the blood corpuscles of the lamb are, after a short time, dissolved and destroyed in the vascular system of a dog, and that the rapidity of this destruction appears to be dependent on the relative quantities.' Such is the final conclusion, which appears to be fully supported by the constancy of the experimental results. I give the figures of one single experiment, as these appear perfectly sufficient.

Experiment III.—Defibrinated lamb's blood injected into a dog to the extent of 49 per cent. of its own blood. Death about 20 hours after transfusion.

Red Blood-Corpuscles.

Method of Estimation.	Immediately before Transfusion.	Immediately before Death.
By direct enumeration . . .	100	56
By colorimetric method . . .	100	59

From all this it may be regarded as an established truth that blood of another species is quickly decomposed in the cir-

culation of an animal. The evidences of this entirely agree, whatever be the method of experimenting. Part of the blood of the animal, into which foreign blood is injected, may also be destroyed after transfusion, and this part is larger according as the quantity of foreign blood transfused is greater, and according as the blood corpuscles of the animal operated upon are less capable of resisting the serum of the blood injected. This circumstance, however, is of subordinate importance.

Can we now explain the severe symptoms which are observed after the transfusion of foreign blood, or even the death which so often follows after larger quantities have been injected?

This question has been answered in various ways. I shall first state the position taken up by Ponfick and Landois in reference to it.

Landois lays particular stress on the multiple emboli, which he considers are essentially formed by the stroma-fibrin and the agglutination of the red blood-corpuscles.

Landois considers that the appearances which are visible in the mesentery of a curarised frog, into whose abdominal vein defibrinated rabbit's blood has been injected, are well adapted to give information with regard to what takes place after the transfusion of foreign blood generally. Extremely feeble circulation; unequal dilatation of the vessels, some of which are almost empty, others engorged with blood corpuscles; large masses of agglutinated blood-cells of the rabbit, which slowly roll along, and remain hanging at the distributary branches of the vessels, thus producing contractions and indeed obstructions of these vessels; afterwards the emigration of red and white blood-corpuscles from the vessels at this same spot – all this comes into notice. Landois gives several drawings, which were made from preparations from a dog into which lamb's blood had been transfused. These show that in fact considerable disturbances in the circulation of the blood in the vessels of the animal, and not unfrequently ruptures of the vessels, take place. From the changes in the circulation there result also further injuries: in some vessels, anæmia, in others, thrombosis, penetrability of the walls, transudations, and even real inflammations. The death of the animal, into which a sufficient quantity of foreign blood has been injected, '*is caused by*

coagulation within the vessels and obstruction of them, resulting from the dissolution of its own or of the foreign blood corpuscles, or of both.'

In opposition to these views, Ponfick denies most decidedly the importance of the obstruction of the vessels. He does not at all admit that this obstruction is ever frequent and extensive, and maintains that many coagula are of post-mortem origin. His opinion culminates in the statement that '*not one of all the media employed, when injected into the vascular system, produces coagula in and by itself.*'

On the other hand, the disease of the kidneys is considered by Ponfick to be the main cause of the suffering and death, the latter being brought about by the suppression of the secretory activity of these organs.

On the whole, Landois appears to be right—positively, in laying stress on the disturbance of the circulation; negatively, in regarding the disease of the kidneys as of little importance. The silence of Ponfick under the attacks of his opponent must be held to speak in favour of the latter. But there comes into notice another factor—on which Worm-Müller lays great emphasis—the altered condition of the vascular wall. That such a disturbance of its nutrition takes place as cannot yet in its nature be satisfactorily defined, Worm-Müller infers from the appearance of genuine hæmorrhages, in which uninjured red blood-corpuscles are exuded. This fact is fully established. The slight after-hæmorrhages, noticed by Panum, from the wounds of animals, into whose vessels foreign blood had been injected, deserve in this connection much attention; as also do the effusions of blood into all the organs of the body, which are not to be looked on as rare occurrences. Landois, it is true, attaches no importance to this idea: he adheres firmly to the mechanical conditions, and attributes to increased pressure and collateral fluxion in the unobstructed vessels the rupture of these vessels; and, in order to explain the persistency of the bleeding from the wounds, he insists on the circumstance that the blood mingled with foreign blood cannot form a firm clot. It is now scarcely possible to decide definitively what is the relative value of these individual conditions; but, when looked at from the general points of view furnished us by the investigations of

Cohnheim, it can scarcely admit of a well-grounded doubt that, in fact, a greater penetrability of the vascular wall is to be expected so soon as the disturbances of the circulation described by Landois have occurred.

The following may be regarded as a summary of our present knowledge of the subject:—

Along with, and by means of, the dissolution of the red blood-cells introduced into the body of another species of animal, there ensues a considerable disturbance of the circulation, which is characterised by the blocking of a larger number of vessels, and by the exit of the contents of the vessels into the surrounding tissues. The tissue nutrition becomes in the whole organism less perfect. Perhaps—Landois enforces this as a secondary idea, it is true—the potassium compounds which have been set free by the decomposition of a large number of red blood-corpuscles must be taken into consideration, especially if their elimination by the kidneys is, as we may surely be permitted to assume, hindered by the impenetrability of these organs, which has been demonstrated by Ponfick. Under certain conditions, the decomposition, in the foreign serum, of the blood corpuscles of the animal operated on may not be entirely without some influence, at least at the time when the fullest activity of its own blood is demanded, in order as quickly as possible to dislodge the injected blood and repair the disturbances caused by it. To refer the whole to insufficient activity of the kidneys is inadmissible; apart from all other considerations it is forbidden by the brief space of time—only a few hours—within which, after transfusion of large quantities of the blood of another species, death ensues. On the other hand, the obstruction of the kidneys is of importance, in so far as by it a quick removal of decomposition products is prevented, which, in themselves (e.g. lime salts), or purely mechanically (e.g. urea, &c.), are calculated to render nutrition more difficult, and perhaps even in great concentration to make it impossible.

The *reactionary symptoms*, which are seen after transfusion of lamb's blood into human beings, have been favoured by Landois with a tolerably precise physiological examination. I content myself with mentioning only a few essential points.

No one, who has once seen a transfusion of lamb's blood from the carotid of this animal into the veins of a man, will ever forget the great dyspnœa, and the unusual degree of cyanosis, which very soon ensue. It is not necessary to say that we cannot speak of 'plethora,' in the older sense of the word, as a pathological condition in a case like this, in which only an insignificant increase of the vascular contents is present. Landois refers the whole directly to an interference with the circulation of the blood through the capillaries of the lungs, owing to the lamb's blood corpuscles having become globular and agglutinated; and, indirectly, to a change in the nervous apparatus of the lungs, since the mixed blood, containing a larger quantity of carbonic acid on account of its insufficient aeration, produces irritation of the peripheral terminations of the vagi in the lungs, as also of the medulla oblongata. It is quite conceivable that this may be the state of the case. The rapidity with which the whole process is accomplished has given me rather the impression that the primary effect is on the central organs. This, too, would be quite conceivable on the ground of Landois' explanations. The simultaneous increase in the rate of the pulse, which is sometimes so great that it cannot be counted, must rather speak in favour of a change in the energy of the nerve centres.

The *increased peristalsis*, betraying its presence by abdominal pain, purgation, tenesmus, is worthy of a few words.

Landois starts from the fact, that disturbed circulation of the blood through the vessels of the intestinal canal causes increased movement of the intestines: compression of the trunk of the abdominal aorta (Schiff), and pressure on the portal vein (Donders), are capable of producing increased peristalsis. The foreign blood entering the right side of the heart in a strong current will, in flowing too abundantly from the carotid of the lamb into the vein of the arm, not only distend this side of the heart, but also will 'become stagnant in the large valveless trunk of the inferior vena cava and in the large hepatic veins. Throughout the capillary network of the liver this stagnation acts against the centripetal current in the portal vein and its branches. The disturbance of the circulation in the vessels of the intestines is caused in this way, and thus

peristalsis is excited.' Blocking of the vessels of the intestines comes on afterwards.

The serious disturbances of the *urinary system* depend on the anatomically demonstrated greater or less degree of impenetrability of the kidneys from the formation of coagula. This always comes into existence with any considerable absorption of foreign blood. Landois considers the cause to be, that a chemical interchange between the acids of the tissues of the kidneys and the globulin-like albumen of the hæmoglobin takes place, by which the latter is precipitated.

If less blood from another species is transfused, there occurs a simple albuminuria, which must be considered as having a relation to the interference with the nutrition of the kidneys; perhaps from changes similar to those which, as is well known, occur in long-continued febrile conditions, and which are often associated with fatty degeneration of the epithelium.

The excretion of biliary pigments, and the increase of urinary colouring matters, suggest only a further using up within the organism of the eliminated free hæmoglobin, which is otherwise unchanged.

There remains still to be mentioned the behaviour of *tissue-metamorphosis* and of the *bodily heat* after the transfusion of blood of another species.

Our knowledge of tissue-metamorphosis is but scanty. From experiments it may be inferred that the loss of weight in dogs after the transfusion of lamb's blood is often rather diminished than increased; at other times the contrary is the case.

With regard to the temperature of the body, the explanation, which Landois gives, in general, of the existence of an increase of temperature, only requires to be added to the facts adduced in connection with another part of the subject.

A marked distinction between the effects of transfusion of blood of the same species and those of transfusion of blood of another species does not exist. As a starting-point for the explanation, the experiment should be chosen in which blood is directly transfused from the artery into the vein of the same animal. The fever that arises under these circumstances must

be attributed to the increased activity of the vasomotor centre. 'The temporary transfusion of a powerful arterial current into a large vein naturally brings with it a considerable over-filling of the large venous trunks, especially the cavæ and the branches immediately opening into them. If the transfusion is now interrupted, then the important task of changing again the abnormal into the normal condition devolves on the circulatory apparatus. This task naturally falls to the vasomotor nervous system, which, from its intracranial centre, regulates the normal blood distribution by means of those movements in the vessels which have been named by me the "periodical regulatory" movements. If the vasomotor centre is thrown into activity under the appearance of more vigorous stimulation, there occurs, first of all, a contraction of all the vessels furnished with smooth muscular fibres, chiefly of the smaller arteries. The consequence of this is, that the vessels of the skin become anæmic, the skin becomes pale and cool, and a feeling of cold takes possession of the body, and is accompanied by shiverings. The skin, however, having become cold, allows less heat to escape from the body by radiation, the heat accumulates in the body, and thus causes a febrile increase of temperature.' This is the opinion of Landois. From this point of view, the production of an increase of temperature by the action of the vasomotor centre fully explains what happens, without requiring any new hypothesis.

The irregularity in the appearance of the fever, its varying intensity, and its disappearance after the lapse of a certain period, is, without anything further, quite comprehensible from the view that it is due to changes in the central nervous system, which are influenced by all the fluctuating conditions of the irritability of nervous apparatus. Thus, as Landois justly remarks, in the case of human beings under pathological conditions, perhaps the anomalous mixture of the transfused blood of a similar species may have some influence on the temperature, and fever may ensue even when a violent disturbance is absent.

The fever that follows the transfusion of foreign blood must be judged according to such suppositions as these. The peculiar nature of the dissolution of the blood corpuscles, the different

mixture of the serum, then also, probably, the manner of transfusion, which is usually, at least in modern times, direct transfusion from the carotid into the vein, are sufficient to explain that here, for the most part, a high (up to 42·8° C.) (109° F.) and, generally, prolonged fever ensues; and, moreover, that it but seldom fails to be present.[1]

The questions regarding *the nature of the blood which may be infused into man* must be decided according to the results of these investigations.

It may now be maintained with great certainty *that the blood of the lower animals is not adapted for this purpose.* As the only question remaining open in this connection, it might be asked whether the result would be otherwise if the blood of apes, instead of that of other animals, were introduced into the circulation of man. Direct experiments, it is true, do not exist, and it is to be hoped that no such experiments will be made. For, though Landois found that 'the nearer two animals stand to each other in their organisation and habits of living, so much the more similar will be the behaviour of their blood, a person requiring transfusion ought not on that account to take a fancy to the quadrumana'—to quote the words of Landois.[2]

Landois transfused blood between animals of the same *order* (dog and cat), of the same *family* (lamb and kid), finally, of the same *genus* (hare and rabbit, dog and fox). Only in the last case is mention made of permanent functional activity of the transfused blood in the body of the animal into which it was transfused; and the repetition of the various experiments was made often enough to secure full proof of his conclusions.

If, therefore, we must restrict ourselves to human blood, it should further be kept in mind that no blood ought to be used without previously testing the state of health of him from whom it is to be taken. If there is sufficient time for preparation, then a better choice can be made than in those cases in which time presses, and we must put up with anything. Robust, not too obese, young men ought to possess blood which, being the richest in blood corpuscles, must also, on that account, be

[1] Hasse, loc. cit., case 31, p. 58.

[2] *Beiträge zur Transfusion des Blutes*, p. 32.

the best. The enumeration of the blood corpuscles, which is easily carried out, furnishes when necessary quite a decisive ground of assurance, and this might be supplemented by a spectroscopic determination of the hæmoglobin, which can be made with a few grammes of blood; the severest requirements would thus be met. A few days before a withdrawal of blood, I cause the man to eat abundant quantities of albumen—two pounds of meat daily; along with this, if the man is accustomed to wine, I make him drink a corresponding quantity of the lighter kinds of wine; the vine dresser's food, usually consisting of a preponderating quantity of carbohydrates, is taken along with the additional food. Thus, at the moment of transfusion, the conditions necessary for well-formed blood are made as favourable as possible.

Here, in Tübingen, I have no difficulty in obtaining excellent human blood; as much as I want is at my command in return for a suitable remuneration in money. In fact, a blood-letting is no great loss to a strong man. I find that those who have formerly experienced the operation are always the most ready to give their blood.

It is, of course, necessary that in the blood-letting we should proceed very carefully, and that after the operation we should bandage the arm under antiseptic precautions, and should see that for some days it is kept at perfect rest. I may remark that, in order to prevent fainting, which, as is well known, frequently occurs in the strongest individuals whenever they see blood, either their own or that of some other person, the individual from whom the blood is withdrawn would do well to place himself in a *horizontal* position. A tolerably large wound in the arm is very advisable, in order that the blood may flow in a conveniently large stream.

Before every transfusion a careful examination of the person who is going to give the blood must be made, in his own interest as well as in that of the individual into whom it is to be transfused. Setting aside those infectious diseases which, even if they cannot yet be diagnosed in their particular form, at least cause a disturbance of the general health quite perceptible to a practised eye, one must specially guard against syphilis and tuberculosis, as also doubtful scrofulous conditions. Blood from a thoroughly diseased person must never be used.

The blood flowing from the vein is to be collected in a vessel, which must not be too small, and, while it is still flowing, it must be stirred and defibrinated. Great care must be taken that this vessel be not only quite *clean*, but also perfectly *dry*. The stirring must be continued until the dark colour of venous blood has given place to a bright red one. Now is the time to filter. For this purpose fine linen in several layers, or satin from which the dressing has been removed, may be used. Of course the filter, which must not be too small, should not be previously moistened nor afterwards squeezed. A considerable quantity of blood is lost. I calculate that I generally obtain for actual disposal about 60 per cent. of the blood withdrawn; this must be taken into consideration in calculating the quantity which it will be necessary to draw.

I know very well that the loss mentioned will appear to many too great—in experiments on animals the loss is always much smaller. But in transfusions for therapeutic purposes I filtered through four layers of linen; and for about 500 grammes of blood, which had been obtained by venesection, I used two middle-sized filter funnels. It is possible that I was over-cautious.

The blood, as it drops from the filter, is best collected in a long-necked flask, placed in a vessel filled with water, heated to the temperature of the body; when the filtration is ended, the flask is closed with a ground-glass stopper, and the air is thus excluded from the blood obtained. If, as is generally the case, the blood is to be used immediately afterwards, then, by subsequently pouring warm water into the vessel in which the flask stands, the desired degree of heat is attained.

The temperature at which the blood ought to be transfused is especially important when the subjects of the operation are enfeebled persons. With stronger persons it is of less consequence, and the quickness of the injection is of greater importance.

Panum says that if the temperature of the blood be about 20 C. (68° F.) a rigor may occur, but otherwise there are no important effects: this is certainly quite correct with reference to experiments on animals. But if one has to treat a patient whose nervous system must be guarded from every

shock, then, taught by my own experience, I would advise great caution,[1] especially if the blood is to be transfused somewhat quickly. If it is really practicable to transfuse slowly and regularly, then the heat of the blood is of less importance; on this point, too, I can refer to my own experience.

To inject the blood *slowly* and *regularly* is generally the most important matter in the operation. Even a very transient over-filling of the heart may lead to serious results.

Panum, who, in his time, most emphatically enforced this point, insisted on a previous depletion, or, at least, the opening of a vein, as a safety-valve. Now when the doctrine of plethora has fallen to the ground, and we have become acquainted with the uncommon capacity of the vascular system to adapt itself to variations in the quantity of its contents, this precaution is no longer required. The other, however, stands to reason. Physicians have, in various ways, sought to find out means of preventing or rendering impossible an over-distension of the heart.

In the first rank may be mentioned *arterial* transfusion, which is specially recommended by Hueter. The great resistance presented by the capillaries renders it, in fact, impossible to introduce such a quantity of blood as could not be controlled even by a heart capable of but little action. Besides, arterial transfusion has further undeniable advantages. The blood, as it passes through the capillaries, is once more subjected to filtration, which, taking place in the body itself, keeps back all the elements in it which might block up the vessels—particles of fibrin which might possibly have passed through the linen filters, air bubbles, agglutinated blood corpuscles. If the blood is injected into the veins, then the filter must be supplied by the lungs—certainly a less favourable locality than the area of distribution of a systemic artery. The radial and posterior tibial are preferred by Hueter. In arterial transfusion the blood can hardly ever flow to the heart of a temperature different from that of the body; a distension of the right ventricle by over-filling is quite prevented.

Here we have a stately credit; let us see what stands against it as debit.

[1] See Jürgensen, loc. cit. p. 24.

There is first the exposure and ligature of an artery against that of a vein. It can scarcely be maintained that the operator requires greater skill for this operation; on the contrary, the inexperienced surgeon will, according to my opinion, in operating on a vein, more easily be thwarted in the object of the operation. There remains only the circumstance that the ligature of an artery is generally regarded as a more serious operation, and is, therefore, gladly avoided. But it is true that this is always a less important matter for the patient into whom the blood is transfused; for Völckers[1] justly remarks that the ligature of the radial and posterior tibial is scarcely to be taken into account when compared with the dangers caused by the disease on account of which transfusion is made.

A further objection to arterial transfusion is, that the capillary area supplied by the artery into which the blood is injected becomes too much distended; swelling of the hand or of the foot, and, under too strong pressure, rupture of the delicate vessels, and consequent hæmorrhage, may ensue. I once saw this actually occur in a case in which Völckers performed with me an arterial transfusion into the radial; in spite of the greatest care, genuine extravasations were produced; the necessary pressure increased so much that the fine sensibility to the pressure applied was lost. Moreover, coagula were formed in and around the cannula, so that it was necessary to interrupt the transfusion sooner than was intended.

This case was a peculiarly difficult one; the nutrition of the whole organism had suffered severely, there was extreme want of blood, and the vessels proved to be particularly brittle. I have mentioned this case in order not to be guilty of an unjustifiable contradiction of Hueter. The latter[2] says that he has injected as much as 1 lb. of blood through the capillaries of the hand; and that, in his last twenty transfusions, he had no fear of over-strong pressure, a fear which he himself at first had. He calls particular attention to a fold or bending of the artery, which easily occurs near the point of the cannula whenever it is pushed towards the hand by strong pressure on the piston of the syringe; for this is quite possible if large

[1] Jürgensen, loc. cit. p. 55.

[2] *Kritisch-antikritische Wanderungen*, p. 173 et seq. Leipzig, Vogel, 1876.

stiff syringes, which must be managed with both hands, are used; it does not occur if, with an easy-working syringe, one hand is kept free in order to hold the cannula in the right position, in the line of the axis of the artery. I am unable to confirm Hueter's statements from want of any experience of my own, but of course I do not doubt their correctness when so positively expressed.

It remains for me still to mention the as yet unsupported opinion of Köhler, who, on the ground of his own theory, considers himself warranted in entirely rejecting arterial transfusion of defibrinated blood.[1] In overweening confidence his conclusions leave nothing to be desired; but, besides what has been already generally urged against his views, we can refer to the experience of Hueter and the numerous experiments of Landois, which are scarcely calculated to serve as a support to the opinions of Köhler.

Transfusion into the veins, with its advantages and objections, comes next to be discussed.

It cannot, and ought not to be denied that in transfusing into veins it is more difficult to inject the blood steadily, and that a weak heart is more endangered from over-filling, though it be only transitory. Everyone who has really, in serious cases, transfused in this way knows that it is necessary to be extremely careful, and that some one thoroughly experienced in feeling the pulse must constantly watch the activity of the heart, in order that the flowing in of the blood may take place in the right manner. Transfusion from the burette, so strongly recommended by Landois—of which I shall again speak more particularly—enables us to overcome these difficulties.

The capillary network of the lungs serves, in venous transfusion, as a filter for the foreign bodies that may be contained in the blood. Among these, *air* is specially dangerous, whenever a large quantity of it makes its way into the veins, the right side of the heart, and the lungs. It would be wrong if, trusting to the results of the experiments on animals, one should take less care to prevent the entrance of air than was formerly the case. For though a small air bubble, which

[1] Loc. cit., especially p. 57 et seq.

happens to get into a vein remote from the heart, may be harmless, yet if fear of the occurrence of this once vanishes, then the small air bubble may very easily become a large number; and it ought never to be forgotten that a feeble individual, whose life trembles in the balance, often enough receives serious injury from very little.

The warning of Landois and Ponfick, whose views Fischer [1] has also adopted, deserves to be heard.

The injection of smaller or larger coagula, which may lead to pulmonary emboli, is possible; but with a little care it may certainly be avoided. Flocculi of fibrin, which have passed through the linen filter, agglutinated blood corpuscles, extremely fine particles of dust are the utmost that will be injected along with the blood; whether these are capable of causing any danger, even where the lungs are diseased, is, in my opinion, doubtful.

The danger of phlebitis must not be too highly rated; it may be regarded as worthy of less consideration than that of the exposure and ligature of an artery; at all events it must be regarded as only of equal importance even by the most enthusiastic adherents of arterial transfusion.

All things considered, the *pros* and *cons* of the two rival methods may fairly well balance each other. Arterial transfusion, in my opinion, is more easily carried out, and requires less care, but involves the loss of an artery; still I would even prefer this, in serious cases, if the use of the burette, according to the proposal of Landois, had not removed the chief cause of danger and the peculiar difficulties of transfusion into the veins. I must at least confess that I was agreeably surprised when, for the first time, I made use of this extremely simple apparatus, and saw the transfusion proceed as the purest physiological experiment without fear or anxiety, and without trouble or any feeling of oppression or dyspnœa in the patient. There is a difference, which appears quite astonishing, between the employment of the syringe and that of the burette, even when the former is managed by as sure and practised a hand as was, in my earlier cases, at my command. The force of gravity,

[1] Volkmann's *Sammlung klinischer Vorträge*, No. 113.

as the propelling power, which can be made greater or smaller by raising or lowering the burette and the surface of the fluid contained in it, and the increase or diminution of the resistance by turning the stopcock at the lower end of the burette, allow of perfect regulation and such a uniform injection of blood as is otherwise impossible. Moreover the security against the introduction of air and coagula is much greater. Since the cannula in the vein remains constantly in connection with the vessel containing the blood—there is no need of any interruption—the transfusion can at once be carried out to the end.

Arterial transfusion, in certain circumstances, may be the only possible method that we can employ. When the operation must be performed in cases where there is a high degree of anæmia and a great accumulation of fat beneath the skin, an attempt to find a suitable vein is often unsuccessful. This will frequently happen to others as it did to Völckers and myself in the second of our cases. Latterly Landois has insisted that, in certain circumstances, *centripetal* arterial transfusion must be practised. I shall afterwards speak of this. The method of transfusion, by injection into a vein, must first be described.

The vein is laid bare by an incision, in the line of its axis, through the skin, and is completely separated from the surrounding tissues for about two inches of its length. After the incision through the skin has been made, it is best to work with blunt instruments (the handle of the scalpel, forceps, &c.); four ligatures are then passed under the vessel (those prepared from catgut are less desirable than those prepared from strong waxed silk threads, as the former slip easily).

Meanwhile the blood prepared, as formerly described, is put into the burette, graduated to 100 c.cm., and which is cut off evenly at its upper end, and at its lower end has a simple ground-glass stopcock. In pouring in the blood it is desirable to use a small funnel, the point of which rests against the inside of the burette, so that the blood may flow without frothing. Attached to the protruding cylindrical exit tube, below the stopcock, is an indiarubber tube, having an inside diameter of 1 to 2 mm. ($\frac{1}{25}$ to $\frac{1}{12}$ in.), which, at its other free end, holds the cannula which is introduced into the vein. I use a tube about 3 feet long; Landois uses one about a hand's length;

for operations at the sick-bed the longer one is more convenient, especially in private houses. The cannula is made of glass; its length is 3 to 4 cm. (1 to $1\frac{1}{2}$ inch), and it is bent at its lower end into a knee with a smooth drawn-out point, and made with a slight bulging near the point. A number of such glass tubes of various thicknesses must be kept ready, so as to be easily obtained when needed; the opening has a diameter of $\frac{1}{2}$ to 2 mm. ($\frac{1}{50}$ to $\frac{1}{12}$ in.)

When the burette is so far arranged, the patient's vein is first ligatured at its peripheral end. The vein is then raised by one of the other ligatures, and an opening is made with a pair of Cooper's scissors. Into the valvular wound thus made the cannula of the burette is introduced, both the tube and the cannula having been previously entirely filled with blood by fully opening the stopcock. As soon as some blood has issued from the cannula it is certain that no more air is contained in the whole apparatus, and the stopcock may be closed. The cannula which has been introduced is now, by means of the second ligature, firmly fixed; the stopcock in the burette is then more or less widely opened, and the transfusion of blood begins. A pressure of 6 feet can be easily obtained, by means of which a quick transfusion of the blood can be effected if required. In serious cases, in which every shock to the nervous system must be avoided, I have preferred to do the exact opposite—to transfuse so slowly that only $\frac{1}{2}$ oz. at most has been injected in a minute. Panum[1] allows 3 ozs. as the maximum in that time. The blood of the one person flows so slowly, but yet so constantly, into the circulation of the other, that I consider the formation of coagula around or in the cannula to be impossible, as the cannula itself is being continually bathed by defibrinated blood. The entrance of air bubbles is quite as entirely and easily prevented by pouring additional blood into the burette at the right time. In order to exclude little particles of dust, which might settle on the small surface of the fluid in the burette, I put an indiarubber stopper loosely on the top of the burette. The only thing that must be thoroughly attended to is to take care that the indiarubber

[1] *Virchow's Archiv*, vol. lxiii. p. 36.

tube does not become bent at any point; even an insignificant narrowing of its lumen by bending, perceptible only on close examination, hinders the outflow enormously. I bring this prominently forward because such a delay in the operation once occurred to myself, and for a long time I vainly sought a reason for it.

Before transfusion, the burette, indiarubber tube, and cannula are washed out with a fluid which does not injure the red blood-corpuscles. I use for this purpose a $\frac{1}{2}$ per cent. solution of chloride of sodium, and afterwards wash them in the same solution. I allow about one litre of it to run through them before and after the operation.

The burette itself I fix, during the transfusion, in an iron retort ring, which is movable horizontally and vertically. When the desired quantity of blood has been transfused, the vein into which it has been injected is tied at the end next the heart by means of the third ligature, and, if necessary, with the help of the fourth; the part containing the cannula is then cut away and removed, and the wound dressed antiseptically. A few sutures may be introduced, though I have not seen much advantage gained from doing so; but, on the other hand, I consider it imperative to cut off the part of the vein containing the cannula, in order to remove all foreign bodies from the wound. This measure is also urgently recommended by Hueter.

Arterial transfusion is carried out in exactly the same way. In it, too, according to the opinion of Landois, the burette can be employed, with only this difference—that a longer indiarubber tube must be used. A pressure of about nine or ten feet is sufficient. If a syringe is to be used, Hueter recommends a small one, holding about three-quarters of an ounce, which should work easily. The stoppage of the backward stream from the artery may be conveniently effected by raising up the vessel with a thread placed in front of the cannula until a bend in the artery is produced. By this means so much blood is forced back into the cannula that, on the renewed introduction of the syringe, no air can enter. It is true this constant introduction and removal of the syringe is troublesome; for, in a transfusion of 17 ozs. which Hueter performed in this way, the syringe was removed and again replaced at least 25 times.

If one has sufficient assistance a larger syringe may very properly be used. It is only necessary, as Hueter remarks, to avoid bending the artery, which causes great resistance.

I may appropriately here make a few remarks on transfusion syringes in general. Syringes with glass barrels are justly preferred, as they can be cleaned with greater facility and certainty. Particular care must be taken to see that the piston fits precisely, so that regular and easy movement of it may be made. The covering of the piston deserves great attention; care must be taken to prevent small fragments of it becoming detached, which might easily happen after long disuse. The application of too much lubricating oil is also to be avoided.

Among peculiar contrivances may be mentioned the 'air catcher' (*Luftfänger*), described by Eulenburg and Landois.[1] This is a drum to be attached to the usual syringe, the entrance tube of the drum being placed at the hinder and upper edge of the cylinder, while the exit tube is placed at the front and lower edge; the latter holds the usual cannula to be placed in the vessel, and projects, with one end slightly bent downwards, a little way into the drum. In transfusion the syringe is so held that the entrance tube always remains turned upwards; the passage of air is thus prevented, since it always seeks the highest point, whilst the exit tube of the blood is situated quite below. Only by very violent emptying of the syringe can air be forced in.

Taking advantage of the fundamental idea, Uterhart has accomplished the same object still more simply, without inserting an intermediate piece, by removing the exit tube of the syringe from the middle to the periphery. A female screw attached to the piston rod permits us to exclude from use a larger or smaller part of the barrel, so that it becomes impossible to empty it entirely, an arrangement which is exactly similar to that met with in several of the Pravaz syringes. Nothing more is required than that the exit tube should be held downwards, and that, by means of the female screw on the piston rod, a sufficiently long portion of the lower end of the

[1] Loc. cit. p. 63.

barrel should be made inaccessible to the piston, in order to prevent with certainty the exit of air.

Besides a large number of modifications of the transfusion syringe, there are not a few forms of apparatus constructed with a great deal of ingenuity for direct and indirect transfusion. It would require too much space to describe these. Anyone who takes an interest in this matter will find a description of most of them in the works of Belina-Swiontkowski. In practice none of these instruments are of much value. Landois [1] is certainly in the right when he discards them altogether with an ironical remark, and stands forth as the advocate of the maxim, 'The simplest is unconditionally the best.'

How large should the quantity of blood be which is employed in transfusion?

Generally speaking this question can only be answered in an extremely indefinite way; each individual case has its own requirements. But still limits may be fixed rather above than below, which certainly are not immovable, but which may form a sort of general guide.

In the literature of the subject we find not a few cases in which a small quantity of blood was sufficient. Thus, for instance, among the 108 cases contained in the summary made by Landois, in which transfusion was indicated by hæmorrhage during and after confinement, ten had 2 oz. and eight had 3 oz. injected. The result in thirteen cases was decidedly favourable; in two otherwise favourable cases a fatal termination afterwards resulted from other causes; in three cases death ensued in spite of transfusion.

If all the cases of hæmorrhage in parturition were to be regarded as identical in value, then it may be said that those in which the transfusion of blood was small had a more favourable course than the average of the whole number operated on; the latter cases gave 58 per cent. of recoveries, the former gave 72 per cent. But, setting entirely aside the fact that the absolute numbers are much too small to be capable of yielding any certain conclusion, it must also be taken into account that in all transfusion statistics it is impossible to guarantee an

[1] *Principal Work*, pp. 324–5.

actual similarity in the individual cases. Every experienced surgeon and obstetrician teaches that the opinion as to the amount of danger threatened to an individual life by hæmorrhage rests on extremely unstable grounds; the prognosis in such cases can never be fixed with definite certainty. This general maxim is doubly applicable to hæmorrhage from the uterus; the body of a woman is uncommonly capable of resistance. These cases of successful transfusion of so small a quantity of blood, therefore, will be regarded by scarcely anyone as sufficient proof that no more than 3 to 4 oz. of blood are required in order to preserve life when it is ebbing away. Most physiologists and physicians who are familiar with transfusion use larger quantities, and, by doing so, they bear testimony indirectly against the use of smaller quantities. Landois, who does not conceal his distrust of the effects of 1 to 2 oz., expresses his opinion freely; and Hueter speaks still more strongly. Hueter has used from 6 oz. up to 17 oz., and these are about the limits within which I have operated. I might refer to an observation made by me in the case already referred to, where I practised transfusion on account of great anæmia after gastric hæmorrhage. At the beginning of the operation, at 10.31, the pulse rate of the patient, who was then quiet, amounted regularly to 96 beats; it continued so until 5 oz. of blood had been injected at 11.12. It was only after this large quantity of blood had been transfused that it fell to 93. I believe that, in slow transfusion of the blood, a good indication of the minimum quantity to be transfused is found in the sinking of the pulse. It is true many sources of error are at the same time to be avoided, the worst of which is to be sought in the excitement of the patient. The maximum quantity which has as yet been transfused in human beings was that employed in the fourth case of my former communication. Here 9½ oz. of blood were injected into a child six years of age, suffering from morbus maculosus, with severe spontaneous hæmorrhages; the body weight was 13·04 kilos.; thus an amount equal to 17 per cent. of the normal quantity of the blood was injected.

Let us now turn to the last part of our subject, viz. to discuss the *indications in diseased conditions for the application of transfusion.*

As a starting-point, we choose the firmly established fact *that by transfusion of blood of the same species we are able to introduce living and functionating red blood-corpuscles into the body.*

No objection will certainly be made from any quarter against the inference to be drawn immediately from this proposition, that after a *severe loss of blood* transfusion is imperative.

Usually it is insisted on that only a life directly in danger must be preserved by the introduction of new blood. This is certainly the first and most important indication. But I wish to add another, which deserves full consideration. *Even the remote dangers of a severe loss of blood, e.g. fatty degeneration of the most important organs of the body, may be prevented by a seasonable transfusion, and the whole period of convalescence may be shortened.*

Clear as the first of these indications is, the fulfilling of it is difficult. The *time* for performing the operation cannot always be easily fixed. If it is only a hæmorrhage from accessible vessels, where the hand of the physician can close the torn arteries or veins, then the matter is quite simple. After the closure, or while it is taking place, the transfusion ought to be performed, and as much blood transfused as seems necessary to restore or preserve the activity of the brain, the heart, and the respiratory muscles.

It is quite otherwise in the case of a persistent hæmorrhage, or one which may at any moment return, and where local mechanical closure of the injured vessels is impossible. The cessation of the bleeding can only be caused by spontaneous thrombosis, which will not ensue until the blood-pressure, having become less everywhere, has become so also at the point where the vessels are injured. The question in the latter case, therefore, is, whether, with a small supply of arterial blood, and a proportionally more abundant increase of venous blood strongly charged with carbonic acid, the centres will show sufficient vital energy to permit of the continuance of life in spite of the weakness of the heart. It must never be forgotten that increased activity of the heart, with the increased arterial pressure proceeding from it, is well adapted to carry away a thrombus not firmly fixed, or to prevent the increase in size of one in the course of formation.

In such cases, therefore, all means that lead to increase of arterial pressure should be employed only with great caution, and not beyond the bounds of urgent necessity. Transfusion should, of course, only be resorted to when all other means are exhausted; and even then it remains merely a hit or a miss, as one can never know when the right moment has come. It is possible that in cases of this kind the new method proposed by Ponfick,[1] on the ground of his experiments on animals, and which in three cases has been already practised on man, may be preferable. Blood, which had better be defibrinated, is injected through the narrow tube of a trocar passed into the abdomen, and by slow absorption is taken up into the circulation; 7 to 12 oz. were injected. The reactionary symptoms consisted only in slight fever, continuing for a day. Further experience of this kind of transfusion, which I mention here only because it was first practised by a highly estimable and earnest investigator, must be left to the future.

[Hayem has published, in a recent number of the 'Deutsche Medizinal-Zeitung' (Oct. 30, 1884), the results of an extensive series of experiments on peritoneal transfusion. He found that, in the case of the dog, when the amount of blood injected does not exceed $\frac{1}{30}$ of the body weight, one half is absorbed in twenty-four hours, and the whole within four or five days. Peritonitis does not occur unless when the blood of another species is injected, but even then it is never fatal. Further, the blood seems to be absorbed, without undergoing decomposition, by the lymphatics, and is transmitted through the thoracic duct to the circulatory system, where it appears to behave precisely as if it had been directly transfused. Hayem claims for this method of transfusion that it is quite as efficient therapeutically as other methods, while it possesses the advantages of being easier of performance and freer from serious local effects.—*Transl.*]

In addition to, and along with, the application of cardiac stimulants, the so called *auto-transfusion* [2] comes to be con-

[1] 'Ueber ein einfaches Verfahren der Transfusion bei Menschen,' *Breslauer ärztl. Zeitschrift*, 1879, No. 16, p. 165.

[2] See Lesser, 'Transfusion und Autotransfusion,' *Volkmann's Sammlung klin. Vorträge*, No. 86.

sidered. The fundamental idea of this is, that, in one suffering from hæmorrhage, the chief point is not so much that the requisite quantity of blood is wanting, as that it is wanting in the right place. The object sought by it is to set in circulation the blood accumulated in the veins of the upper and lower extremities, abdomen and thorax, and to conduct it into the arteries, from which it may then flow in equal proportions to all the organs of the body. The means taken to attain this object consist in kneading the limbs, swathing them in elastic bandages, and by this means pressing the blood out of them, and in propelling that, which is thus forced into the large venous trunks, farther into the right side of the heart, by compressing the chest and abdomen. The quantity of blood which may be recovered for general circulation in this way cannot be estimated with any certainty. In the extremities there is but a comparatively small quantity of blood. Paul Bruns [1] calculated on an average that the blood of the leg amounts only to 3·8 per cent. of the weight of the limb, and this calculation quite coincides with Ranke's statements. It is, however, a well-known fact that the veins of the abdomen are very capacious, and in auto-transfusion it is an essential question whether we can, and whether we dare, carry out massage of the abdomen and compression of the chest to a sufficient extent. That this is impracticable in hæmorrhages of the lungs, stomach, and intestines (to mention only the usual kinds of hæmorrhage) requires no long demonstration. On the other hand, hæmorrhage from the uterus certainly presents a more hopeful field for this treatment.

To sum up the whole once more in a few words: in cases of hæmorrhage from accessible vessels, transfusion must be made soon after their closure; in such as do not admit of direct stoppage of the blood, the operation must be begun only when the probable formation of an actually obstructive thrombus may reasonably be inferred. The operation should therefore be delayed as long as it can be with safety.

The *quantity* of blood to be transfused must also be decided according to these considerations. In cases of hæmorrhage,

[1] 'Experimente über die Blutgehalt der menschlichen Extremitäten u.s.w.,' *Virchow's Archiv*, vol. lxvi.

where the wounds in the vessels are already closed, it is right to exceed what is directly necessary for the preservation of life, so far as it is required for the purpose of shortening the period of convalescence. An increased blood pressure, that is, a pressure of normal height, cannot but be desirable here. The case is different in injury or rupture of the vessels where the closure is not very strong; for the reasons already mentioned, it will be necessary to restrict one's self so far as to inject only so much blood as is required to preserve sufficient activity in the vital organs.

In transfusions, which are to be practised under such conditions, there arises a further difficulty in carrying them out; a difficulty which increases the longer one has to wait. I am entirely disregarding the chirurgico-technical side, although this also is to be considered; for, as has been already remarked, it may be impossible even for a practised operator to find a vein, scantily filled with blood, where there is much corpulence. Much more essential is it to have due regard to the excitability of the nervous centres themselves; Landois justly devotes to this subject a special chapter.

After a severe loss of blood, the circulation is slowed throughout; the arterial pressure sinks very much so soon as a certain limit is overstepped; the difference of pressure between arteries and veins becomes smaller, and the quantity of blood which is conveyed to every individual organ within a given time diminishes more and more. 'In the highest stage of acute anæmia, the excitability of the medulla oblongata is kept up by only tiny, slowly circulating streams of blood, which pass through the capillaries of this vital and most important group of centres' (Landois). If a larger quantity of blood is conducted in a short time through a vein, then there occurs first of all, along with increase of pressure, a stasis of the blood in the large venous trunks and in the feebly acting right side of the heart. The difference of pressure between arteries and veins becomes still smaller, and the circulation of the blood still slower. Thus, though it be but for a few seconds, a further interruption of the circulation may take place in the medulla oblongata, which, with the already extremely limited nutrition of this organ, may be enough to entirely stop its function.

I can readily agree with Landois, who explains in this way the fatal cases which occur with symptoms of asphyxia after venous transfusion in extremely weak patients.

Landois in these circumstances recommends *arterial*, and especially *centripetal* arterial, transfusion. Blood is injected into an artery (the radial or one of equal calibre) towards the aorta, the valves of which close; and the blood at the commencement of the aorta, being thus placed under high pressure, escapes into the side branches, and flows through the carotids and the subclavians to the medulla oblongata, to which it brings immediate help. In order that blood may not press into the branches of the descending aorta in too great quantity Landois advises that both femorals should be compressed, and that moderate pressure should be applied to the abdomen. Too little blood must not be used—10 to 20 oz. at least. The technical difficulties are not greater than those met with in exposing and ligaturing an artery generally. As the pressure in the aorta is lower than normal, it can be easily overcome by means of a large tight syringe, capable of containing at least 6 or 7 oz.; the burette, furnished with a long tube, will even be sufficient.

Landois [1] communicates experiments by which, at all events, the practicability of the proposal is proved. Whether centripetal arterial transfusion offers actual advantages, and whether it may be practised at the sick-bed in all cases without injury, I must leave to be decided by further experience. Landois himself remarks that, during the injection of the blood, a diminution of the activity of the heart occurred; and when the injection was made into arteries near the heart this diminution was accompanied by moderate dyspnœa.

However clear, theoretically considered, the value of centripetal arterial transfusion may be, the effects described appear to me by no means unimportant: an enfeeblement of the cardiac muscle, and greater penetrability of the pulmonary vessels—these form a very critical complication.

I think that I am convinced that venous transfusion by means of the burette is exactly suited to these cases, as it admits of a very slow and steady injection; venous transfusion

[1] See principal work, pp. 114, 357, and *Beiträge*, &c., p. 32.

by means of the syringe is, indeed, very difficult to carry out. The large quantity of blood required will also contribute to circumscribe the domain of centripetal arterial transfusion. With unclosed wounds of the arteries it would for this reason be dangerous.

In practising the usual kind of transfusion into the veins, besides the great rule to infuse slowly in such cases, it is also advisable to attend to another one—let the heart be somewhat stimulated. Wine, if the patient can still swallow properly, or, whenever this is no longer possible, subcutaneous injection of oil of camphor[1] under the skin of the back, in a single dose of 5 Pravaz syringefuls of the officinal preparation, each in a separate place in order to facilitate absorption, is urgently to be advised. It is imperative that constant watch be kept over the activity of the heart and of the respiration. In conditions of extreme weakness let the operator beware of an excess of blood. Such an excess may become dangerous by bringing about too sudden a change in the conditions of nutrition of the nervous system, and induce the 'shiverings' described by Panum. Besides, the possibility is not excluded, that an increase of temperature may follow it.

On the other hand, if the immediate danger to life is successfully combated without transfusion, the patient remains in a deeply exhausted state, and requires a long time for recovery. Of course, we must always exercise discrimination, and not merely say that every man who has lost blood must directly receive new blood in its place. It is pretty frequently seen—the daily experience of the obstetrician furnishes the best proof—that severe losses from hæmorrhage are made good in a comparatively short time. All that is required is a good appetite, healthy digestive organs, and not too great age. But the case is somewhat different when hæmorrhages from the lungs and the stomach are considered. As a rule, the sufferers from these are individuals who were not endowed with full bodily power of resistance previous to the commencement of the hæmorrhage. The appetite was already lost, food was taken only in small quantities, perhaps there was not even a sufficient supply given. Then came the hæmorrhage. For a long time

[1] Ph. Germ. Ten per cent. solution of camphor in olive oil.

afterwards the patient was restricted to low diet, perhaps to a purely fluid one; the more severe the hæmorrhage, so much the more strictly was it necessary that this regimen should be carried out. In hæmorrhages from gastric ulcers, at least, the rule to confine the patient to a diet which only satisfies the essential demands of nature will hardly meet with contradiction. Frequently recurring hæmorrhages from the lungs, in my opinion, often demand the same treatment.

If at length food that has hitherto been withheld may be given, to bring about a quick restoration of what has been lost, then a diet unrestricted in its choice of foods, even if it has at command all the resources of the culinary art, is often far from being successful in attaining the desired aim. The appetite is wanting, and also the power to digest.

The acute anæmia is but slowly or not at all removed. Its consequences, as fatty degeneration of the heart, show themselves most distinctly and painfully, and we get marasmus. The more the general nutrition had failed before the hæmorrhage, so much the more is this marasmus to be feared, so much the more difficult is it to eradicate the anæmia which has now become chronic. Here the transfusion of fresh blood may be very helpful. With regard to hæmorrhages proceeding from pathological changes which are not progressive, or, at least, not necessarily so, the indications for transfusion appear to me incontestable. I include in these, hæmorrhages from a gastric ulcer and those from a cirrhotic lung; the latter, as is well known, not unfrequently lead to the severest losses. The decision of the physician in each individual case must be mainly guided by the question whether there exists the probability of a malignant or of a non-malignant form of the disease which may be permanently removed.

Such a decision often makes very great demands on the diagnostic capacity, and must often enough be arrived at with only a small amount of probability. I shall leave the disease of phthisis out of the question in this place. If it is thought necessary to practise transfusion after a hæmorrhage which has arisen in the course of that disease it does not fall to be discussed here. It is difficult to decide as to the advisability of transfusion after hæmorrhage from the lung when it occurs in

the course of a localised chronic disease of that organ, accompanied or not by tubercular infection; the question is not an easy one. With regard to hæmatemesis, physicians are more seldom divided in their opinions, but differences are not excluded by any means. On which side the wavering balance falls depends just as much on the character as on the scientific knowledge of the physician who is called on to give a decision. I should like to direct attention to one thing—the probability, that a correctly and cautiously carried out transfusion can endanger the patient, is small. It appears to me of secondary importance in comparison with the advantage which the operation may bring to the patient. In doubtful cases, therefore, I perform transfusion rather than omit doing so. The possibility of shortening the life of an individual whose days are already numbered is not to be disputed; but, on the other hand, it must not be forgotten that increase of blood also brings with it a greater capability of resistance in the body, and better chances of an ultimate cure. Besides, the importance of a palliative measure, which may, for a short time at least, alleviate the sufferer's pains, should not be lost sight of.

The *period* after hæmorrhage to be chosen for the performance of transfusion for the purpose alluded to must, it appears to me, be dictated by due regard to the definitive closure of the vessels at the place where the bleeding has occurred. According to the experience of surgeons, even a large artery becomes thoroughly closed by an organised thrombus in the course of about 9 days. When this period has elapsed, the physician may confidently proceed to a prophylactic-restorative transfusion. If he has once determined on it, then longer delay appears to be advisable only in those cases in which he is still in doubt as to the capacity of the system to absorb nourishment. If he wishes to put off the transfusion until distinct cardiac symptoms show themselves—as dyspnœa, which is often believed to be asthmatic when it occurs periodically, that is, in the evening, shortly before falling asleep, and in the first hours after awaking—then weeks not unfrequently pass before such symptoms are observed. The patient affected with severe hæmorrhage first feels his own weakness when, after some time, he makes demands on his heart, and which then tells him of

its insufficient strength. Then, however, fatty degeneration is generally already present. Genuine prophylaxis does not wait so long. An enumeration of the blood corpuscles and a determination of the amount of hæmoglobin, even if it were only roughly made, would furnish important information; it would show whether a decided deficiency in the necessary constituents of the blood exists. By repeating this proceeding, all doubt of the necessity of transfusing would soon be removed.

It may be asked, In what manner does such a transfusion act? We might reply that the presence of red blood corpuscles in a definite quantity is necessary in order to enable the functions of all the organs to be carried on in a normal manner. If the blood corpuscles are lost, and if their replacement by the self-activity of the body is not possible, then arises the necessity of a supply from without. But we must not content ourselves with such a very general hypothesis. The newly introduced red blood corpuscles procured from another individual not only effect a mere replacement of corpuscles, but they also furnish the person into whom the blood is injected with a greater capacity for the conversion or assimilation of his nutriment, and give him the opportunity of reimbursing himself for the loss occasioned by the hæmorrhage.

I believe that this view lies strictly within the bounds of our physiological conceptions; at all events, I beg that it may not be confounded with Hasse's view,[1] which Panum[2] justly severely criticises.

I have formerly, in a concrete case, accomplished the result at which I aim.[3] The remarks then made by me, however, appear to have been entirely overlooked.

The case was that of a man, 23 years of age, who, on December 9, 1870, had poisoned himself with a large quantity of phosphorus. Sixty-four days later, on February 11, 1871, I made the transfusion. It is thus recorded:—

'The decreasing fever appeared to signify that the acute action of the poison had run its course. The great question now was to supply the body with the material necessary for rebuilding its tissues. This was practicable only through

[1] 'Ueber Transfusion,' *Virchow's Archiv*, vol. lxiv.
[2] Ibid. vol. lxvi. [3] Loc. cit. pp. 7, 8.

the digestive canal. Of what nature were the changes in the organs controlling assimilation, and what disturbances of their functions had these organs suffered? Some of the glandular cells had assuredly been destroyed, and were not directly to be replaced. But those that remained behind, which had escaped destruction, required, for the due performance of their function, blood from which they could secrete. This blood, as it proceeded from the heart, must be kept under a certain pressure. The therapeutic aim consisted only in an attempt to change the composition of the blood, in order to stimulate the muscle of the heart to greater activity and bring the blood under higher pressure, and to supply the glandular cells with better material for the maintenance of their function. Since our object was to render the assimilation of nutriment more complete and more easy, it was necessary to attempt to impart to the organism the possibility of procuring renewal of its severely damaged tissues. The transfusion of as large a quantity of normal blood as possible appeared, from this point of view, the only measure worthy of a trial.'

The patient, whose blood showed very great changes, received 21 oz. of defibrinated blood into the veins, with a depletion at the same time of 18 oz. from the radial artery. From that hour he improved, because he could again eat. This case must, however, not be plainly called a transfusion in a case of phosphorus poisoning, as Landois [1] himself has named it. It belongs rather to the indication being presently discussed, and appears to me to run parallel in all directions with transfusion after great losses of blood.

In order to remove all uncertainty, I must strongly assert my own belief that the activity of the blood introduced in these circumstances is connected in the first place, and with preponderating importance, with the red blood corpuscles. These supply more oxygen, with the presence of which the excitability of every single element in the body is connected, whether it be nerve or muscle, ganglionic or glandular cell. In quite a subordinate, perhaps an unimportant, way, a direct nutrition by other constituents of the blood, possibly the albumen of the serum, comes into play. Further than that, however, we can

[1] See his principal work, p. 130.

scarcely venture to go in the present condition of our physiological knowledge.

The cases of *chronic anæmia* naturally fall to be discussed now. In general, they may be considered as all alike, but still, in individual instances there are very considerable differences.

In the first place, two large groups must again be distinguished—anæmia arising from a cause that may be combated, and anæmia from a cause that cannot be combated. With regard to the malignant form, transfusion can, at most, have the importance of a palliative measure, and even that only for a short time; when carcinomatous cachexia, renal disease, &c., have arisen, no physician of even average intelligence will imagine that he will be able to remove them by transfusion of blood.

Whether transfusion in *leukæmia*, *pseudo-leukæmia*, *true progressive pernicious anæmia*, *Addison's disease*, or in severe cases of *chlorosis* possesses any importance further than as a temporarily acting palliative measure must be left to the decision of further experience. Experiments are certainly allowable in these diseases, otherwise inaccessible to therapeutics; but in performing them let physicians stand on the ground of simple empirics, and let them not conceal from themselves that a definite scientific foundation is wanting. As spontaneous cures of these diseases do occur, it is not inconceivable that a temporary improvement of the nutrition, which is possible by performing a transfusion, may form the starting-point of a change for the better. That this will not regularly happen, must, as in the application of every empiric measure, be positively expected.

The case of *phthisis* may, under certain conditions, be somewhat different. If an individual suffers from an old affection of the lungs, but in other respects is in good health, and becomes anæmic from an acute hæmorrhage occurring quite unexpectedly, it would certainly be absurd to refuse to perform transfusion in such a case because, in the current language of the country, 'he is consumptive.' There are cases enough of this kind in which the danger was caused by the severe hæmorrhage alone, and in which the local disease, having long ago run its course,

was making no subsequent progress. On the other hand, it must not be believed that it is possible to do anything directly against the pulmonary disease by transfusion. If the physician wishes empirically to make a trial of transfusion in this disease, he must first ascertain, by a close examination of the blood, whether an actual deficiency of hæmoglobin exists. That such a deficiency does not necessarily exist in all phthisical patients, is quite certain (Sörensen, Malassez, Leichtenstern). The operation can hardly be said to promise much. We would previously require to entirely exclude the rapidly progressive forms that are accompanied with high continuous fever and widespread disease of the lungs, and to restrict ourselves to those which have a slower course, in which weakness and want of appetite, along with slight fever, are the prominent symptoms.

The researches of Lesser[1] into the cause of death after *burns* open up a new field for transfusion.

Lesser found that, when the skin is burnt, the red blood-corpuscles undergo essential changes: the connection between stroma and hæmoglobin is broken; the latter is set free and leaves the body by the kidneys, in which organs changes show themselves similar to those which occur after the injection of foreign blood. It was proved that the absolute number of the red blood corpuscles does not essentially diminish—at least in the period immediately following the injury. It appears, therefore, that a burn produces changes even in the blood corpuscles—although to all appearance they remain unaltered in form—and that these changes are accompanied by lessening and even loss of their activity. This occurs in consequence of a considerable and comparatively long-continuing increase of temperature at the seat of the injury. The blood flows through vessels which, along with their surrounding tissues, are heated greatly beyond the normal, and it undergoes changes similar to those which take place when it is heated outside the body.[2]

By experiments on animals which had previously been made anæmic, Lesser established the fact of the physiological injury to the blood of men who have died from burns, and its in-

[1] 'Ueber die Todesursachen nach Verbrennungen,' *Virchow's Archiv*, vol. lxxix.

[2] See above, p. 260.

capability of accomplishing the respiratory exchange of gases. If such blood was injected into an anæmic animal there soon appeared great dyspnœa, which ended in the death of the animal from paralysis of the respiratory and vascular centres.

Besides careful, strictly antiseptic treatment of the burns, the depletory transfusion recommended in such cases by Ponfick appears, according to the above statement, to be rationally indicated.

Experiments on human beings are as yet wanting.

Can the introduction of blood into the vessels *directly nourish* the organs of the body, and entirely, or to a certain extent, take the place of absorption of food from the stomach and intestines?

Even physiologists are divided in their views on this subject; the opinions of Panum and Landois are diametrically opposed to one another. Panum [1] denies that transfusion has any considerable influence. He refers to the fact that the largest possible quantity of serum-albumen contained in the blood does not by any means serve the purpose of the nutrition of the tissues. There is present in normal blood, for that end, only a small quantity of albumen—serum-casein, or, to call it by other names, serum-globulin, paraglobulin, or fibrinoplastin—which is not an integral constituent of the blood, but which only uses the blood as a vehicle.

This reasoning is at present less decisive than formerly, on account of more modern researches into the relation of serum-casein to serum-albumen.[2] Whilst, by the older methods of analysis, only 0·38 per cent. of serum-globulin was found in human blood (Heynsius), Hammarsten now estimates its amount at 3·103 per cent. Should this analysis receive confirmation, then, indeed, a not inconsiderable quantity of the albumen of the transfused serum would be capable of aiding nutrition. Non-nitrogenous substances, as sugar, fatty acids, cholesterin, &c., are contained in the transfused blood in much too small quantities to be worthy of any consideration whatever.

[1] 'Experimentelle Untersuchungen über die Veränderungen der Mengenverhältnisse des Blutes, etc., durch Inanition,' *Virchow's Archiv*, vol. xxix., and in the separate edition of his collected works, p. 219 et seq.

[2] See Hoppe-Seyler, *Physiologische Chemie*, part iii. p. 421 et seq.

Panum, however, supports his opinion still further by his own experiments, from which he not only infers that no nourishment is possible by means of transfusion, but also adduces the reason for this.

First of all, it is established that, notwithstanding temporary variations, a constant, individually definite ratio of the quantity of blood to the weight of the body is maintained. Moreover it is proved that, by complete withdrawal of food, it is not this or that constituent of the blood which specially decreases, but its total amount rather becomes diminished, equally with all the other parts of the body. At the utmost, the serum suffers a small loss in albumen (serum-casein), but even that is not constant. If a transfusion is performed on a fasting animal, then, after the lapse of a few days, when the quantity of blood has been reduced to the original habitual amount (by elimination of water or the passage of plasma into the tissues), there will be found an increase of the red blood-corpuscles in a ratio nearly corresponding to the quantity of blood transfused; at the same time the relative quantity of the solids of the serum will not be materially diminished, nor yet will that of the fibrin. Thus even here a nourishment of the tissues by the red blood-corpuscles and by the fibrin could not have taken place; in proof of this we only require again to consider the small quantity of albumen which has disappeared from the serum.

The loss of weight after a transfusion into a fasting animal is more considerable than before the transfusion. Panum thinks that the presence of a larger number of red blood-corpuscles in the circulation may perhaps increase the inevitable loss of weight, which a fasting animal undergoes, by increasing the absorption of oxygen.

Opinions of individuals differing from him, especially those of Eulenburg and Landois, who likewise refer to results of experiments, are set aside by Panum with the remark that they had not observed the fact that a dog can often live four weeks in a state of complete inanition. 'Beyond that time, indeed, no one has ever succeeded in keeping a dog alive by means of transfusion without any food.'[1]

[1] Panum, *Virchow's Archiv*, vol. lxiii.; p. 4 of the separate edition.

The evidence brought forward by Eulenburg and Landois against this assertion is undoubtedly, as it appears to me, not very satisfactory. Even the original notion of the indication [1] suffers from a certain indistinctness, not to say obscurity. If a quantity of active vital blood is injected into a fasting dog, the state of the case in many respects is manifestly analogous to that induced by a fresh supply of ordinary food, since, with the transfused blood, constituents are directly absorbed which are capable of being oxidised; and thus, *a priori*, the quantity of the oxidising material of the body is reduced proportionately to that of the oxidisable material introduced from without.

What is the theory of the behaviour of this latter material? Is it that it simply uses up and keeps back the oxygen from the tissues of the fasting animal, or that it supplies them with actual nourishment? On that subject as little explanation is given as on the constituents which are to be regarded as specially active. Landois expresses definite views only in his chief work, in which he designates a part of the blood—and indeed the plasma with its dissolved albuminoids—as that which is made serviceable in the body for tissue metamorphosis. Already in his first work he records some experiments.

Into a dog, weighing 3,970·2 grms., there was transfused every second day, commencing on the 6th day of absolute fasting, the blood of another dog, until altogether 21 oz. had, in the course of 18 days, been injected. On the 24th day it died, after its loss of weight, inclusive of the transfused blood, had reached 1,744·6 grms., i.e. 40 per cent. of its weight at the beginning of the experiment.

A second dog, of 5,324 grms. weight, died at the end of the 9th day of its complete fasting; it had lost 2,461 grms., or about 46 per cent. of its weight at the beginning of the experiment.

It is, then, concluded that this control experiment 'scarcely admits of a doubt that the relatively long continuance of life in the first animal must be ascribed to the favourable influence of the repeated transfusions.'

That this conclusion is not tenable is proved by the experimental data themselves. It is a well-known fact, and is men-

[1] Eulenburg and Landois, loc. cit. p. 45 et seq.

tioned even by Landois and Eulenburg, that there are very great relative differences in dogs when under the influence of hunger. Dog I. of F. A. Falck's [1] experiments lived 24 days, dog IV. 61 days. A certain loss in the weight of the constituent parts of the body, the relative greatness of which is constant in death from starvation, is reached in a period that varies very much. Now the *transfusion dog* of Eulenburg and Landois lost in the first 5 *days of complete hunger only* 11 *per cent.* of its body weight, whereas the *control dog in* 4 *days of complete hunger lost* 29 *per cent.*, and *in* 6 *days of complete hunger* 34 *per cent.* of its body weight. No real comparison can therefore be instituted, and the experiment is consequently valueless.

Other experiments in a similar direction have not been made; that is to say, no one has attempted to prove the possibility of keeping a fasting dog alive longer by transfusion than it would otherwise have lived; and this is in reality the kernel of the matter. Landois, however, uses the results obtained by himself and his predecessors as indirect inferences in favour of his own conclusions. More urea is passed by a fasting dog after a transfusion than before it; proofs are adduced of this well-established fact. If more urea is passed, more albumen must also be used up in the body; nothing can be urged against this. Another question, however, is, whether, along with this greater use of albumen generally, there is also a more sparing use of the albumen firmly united in the body. It is quite conceivable that this could not be the case; that, on the contrary, the greater stream of albumen which passes through the tissues causes the metamorphosis of a larger amount of them than would otherwise have been the case. It appears to me that neither the experiments specially brought before us, nor the present position of the theory of tissue metamorphosis admit of a final decision. On the whole, I believe that Panum's opinion is more probable. I do not know whether the circumstance that Landois, in his excellent manual of physiology, does not, when discussing the indications for transfusion, mention that opinion, warrants the conjecture that he himself has taken exception to it.

[1] See *Archiv für experimentelle Pathologie und Pharmakologie*, vol. vii. p. 373.

Panum, in other respects so diffident, maintains that transfusion is rationally indicated in every case of *carbonic oxide poisoning.*

This results directly from the fact that carbonic oxide unites, in the same proportion as oxygen, with hæmoglobin, which then, as the compound with carbonic oxide is the more stable one, ceases to absorb oxygen, and thus to serve the ends of respiration. Here also the first suggestion came from physiologists. Kühne [1] proposed transfusion of blood in carbonic oxide poisoning, and supported his advice by a series of experiments. On account of the great practical importance of the subject, I shall enter somewhat more particularly into the therapeutic question by repeating the essential points of former procedures.[2]

Poisoning with carbonic oxide can happen in two ways:—

1. A large quantity of gas may in a short time be absorbed. Life becomes extinct, without the occurrence of any further demonstrable changes than those due to the formation of carbonic oxide hæmoglobin in the blood. This form of poisoning must be regarded as a pure primary blood poisoning.

2. Carbonic oxide may be absorbed by degrees in a quantity not sufficient to cause extinction of life in so short a period as that mentioned above. Whilst it remains in the blood, secondary changes take place, which, alone or in connection with the poisoned blood, cause death.

The supply of new blood will, in the first case, if it is injected in sufficient quantity, be of essential service. In the second case, this will be far from always so; the disturbances of the nutrition of the vital organs will decide the issue there.

I wish to lay some weight on this distinction, viewed from the standpoint of the therapeutist, since, without theoretically prejudicing anything whatever, it suggests to the practical physician that henceforth, when he has performed transfusion in a case of poisoning by the fumes of burning charcoal, he has not done all that is necessary. The interpretation which the ingenious inventor of this treatment, Kühne,[3] gives to his

[1] *Centralblatt für die med. Wissenschaften*, 1864, p. 134 et seq., and *Physiologische Chemie*, p. 237.

[2] Jürgensen, loc. cit. p. 39 et seq.

[3] *Lehrbuch der physiolog. Chemie*, p. 237, and his earlier communication, *Centralblatt für die medic. Wissenschaften*, 1864, p. 134 et seq.

proposal is rather calculated to help on the misunderstanding. With very few exceptions, which only occur under quite peculiar conditions, the ordinary form of charcoal poisoning is caused by breathing for a long time an atmosphere which contains comparatively little carbonic oxide. The distribution of this gas amongst the blood corpuscles must therefore be entirely different from that which takes place in *experiments* with inhalation of carbonic oxide. As this point appears to me the critical one, I shall discuss it more minutely.

A priori, two views are possible of the distribution of a given quantity of carbonic oxide in a given quantity of blood, as long as the quantity of carbonic oxide is smaller than that which is necessary for complete saturation of the hæmoglobin in the blood.

1. The hæmoglobin in a certain number of blood corpuscles may be completely saturated with carbonic oxide, whilst the remainder is completely unacted on.

2. The hæmoglobin in each individual blood corpuscle may have combined partly with carbonic oxide, partly with oxygen. No single blood corpuscle entirely escapes. The quantity of carbonic oxide in the individual blood corpuscles may be considered either as equal or as varying.

Or, in other words, the question may be thus formulated:—In charcoal poisoning does a part of the blood corpuscles of the organism, or does a part of the hæmoglobin in its blood corpuscles remain active?

The results of experiments certainly approach nearer to the first theory than to the second. With regard to experiments on man,[1] in which pure carbonic oxide was inhaled, this can be confirmed as well in him as in animals. Witter, for instance, after having made his lungs as free from air as possible, inhaled pure carbonic oxide with three or four deep inspirations. There are individual authors who have even gone so far as to bring directly into the discussion the effect of blood saturated with carbonic oxide injected into the veins.

What is the state of the case, however, with the charcoal poisoning as ordinarily observed? It is not possible to form a numerically expressed estimate of the quantity of carbonic

[1] See Friedberg, *Die Vergiftung durch Kohlendunst*, p. 37 et seq.

oxide in the atmosphere inhaled, though the analyses[1] of the fumes of burning charcoal, when unmixed with incalculable quantities of air, show a maximum of 5·4 per cent. and a minimum of 0·52 per cent. of carbonic oxide. From the circumstance, however, that human beings can live and breathe from 10 to 12 hours in air which contains carbonic oxide, it may be inferred, in connection with the results of experiments on animals, that the amount per cent. of carbonic oxide contained in such air cannot have been very large.

The quantity of air inhaled with every inspiration can therefore convey but a small portion of carbonic oxide to the blood. After the absorption of the gas by the fluid of the blood, the chemical attraction of the hæmoglobin makes itself felt, by which a large number of separate corpuscles, furnished with the same power of attraction, moving continuously onwards, come only for a short time in contact with the weak solution of carbonic oxide in the plasma of the blood. I imagine the state of the case to be just as if one passed a slow current of sulphuretted hydrogen, for some time, through a quantity of water containing metallic silver mechanically suspended in it. Even here sulphide of silver and metallic silver will be visible together in one and the same particle of silver. If the respiration of air containing carbonic oxide continues long enough, then gradually an ever-increasing part of the hæmoglobin may be changed into CO-hæmoglobin, and, perhaps, isolated blood corpuscles may become entirely saturated with carbonic oxide. But the circumstance must never be lost sight of, that a part of the hæmoglobin in the blood corpuscles, and not a part of the blood corpuscles themselves, has become inactive.

Another circumstance compels us to this opinion. Kühne found that, even in the blood itself, oxidation of the absorbed carbonic oxide takes place, and so carbonic acid is formed, and, in fact, by the action of the free red blood corpuscles. It is not, however, to be taken for granted that, while the blood corpuscles which contain carbonic oxide are being continuously changed into those which are free from it, each separate poisoned blood corpuscle becomes entirely free from the

[1] See Eulenburg, *Die Lehre von den giftigen und schädlichen Gasen*, p. 107.

gas before the process begins with its companion corpuscles. More probably the oxidation of the carbonic oxide to carbonic acid proceeds intermittently in the individual corpuscles.

It has been demonstrated by Kühne that one-fifth of the whole blood in dogs may be saturated with carbonic oxide without endangering life; indeed, that in a short time the oxidation of the carbonic oxide to carbonic acid is accomplished. Here, however, he was dealing with the action of entirely intact blood corpuscles on poisoned corpuscles. Another question is this, What is the state of things with regard to the oxidising action of half-poisoned blood corpuscles? If one imagines a blood corpuscle whose hæmoglobin is half saturated with carbonic oxide, it is really impossible to see why the oxygen absorbed by contact with the air should not at once have an oxidising action on the carbonic oxide. This will certainly happen; for how otherwise is it possible to explain the serious cases of poisoning with charcoal fumes in which long-continued artificial respiration brought help? If, however, we consider how very small is the quantity of foreign blood, which by its injection produced a rapid cessation of the dangerous symptoms, we cannot help being of the opinion that the unattacked blood corpuscles must be able to provide for the oxidation of the carbonic oxide to carbonic acid in a very much shorter time than the half-poisoned ones. In my case, in which at least half of the original quantity of the hæmoglobin remained free, about $\frac{1}{23}$ (4·3 per cent.) of the whole blood was freshly transfused, and in a few hours all danger to the organism was removed. How long is it, on the contrary, before the dangerous symptoms are overcome by artificial respiration alone! For a right understanding of the rapid action of transfusion it has still to be pointed out that this action must be a progressive one; for the blood corpuscles, which have been gradually freed by the originally transfused blood, set free, in their turn, the poisoned blood corpuscles around them.

Let us now resume the consideration of what therapeutics has to do in a case of charcoal poisoning. It is as follows:—

The physician must see to it that the carbonic oxide in the blood of the poisoned person is oxidised to carbonic acid in as *short a time as possible*, and that the occurrence of serious dis-

turbances in the nutrition of the essentially vital organs is hindered.

With regard to these secondary disturbances, I agree with the opinion of those who ascribe them to the negative action of the carbonic oxide—hindering the absorption of oxygen. It is true the irritative action of the gas on the inhibitory nervous mechanism of the heart and on the vasomotor nervous centre has been demonstrated.[1] But these deviations from the normal are insufficient in themselves to produce serious disturbances; moreover, the latter are frequently wanting. The hypothesis of a negative action of the carbonic oxide appears to me more probable because it explains how, in very acute cases of poisoning—for instance, in experiments on the lower animals—even though a large quantity of the poison is introduced in a short time, no secondary changes occur; while in those cases in which a relatively small quantity was absorbed throughout a long period, these secondary changes appear. A small supply of active oxygen to the tissues will necessarily result in producing in the tissues a gradually increasing accumulation of raw products of oxidation, which are difficult of solution, and which, disturbing the endosmosis in the tissues, may suffice to cause a possibility of changes in the structure, or at least in the function of the various organs. I think it is not at all unlikely that convulsions, when they appear late in cases of slow poisoning, are to be attributed to such alterations of the conditions of diffusion in the brain, and therefore ensue (as, according to Voit, convulsions in uræmia do) without giving any ground for saying that here there is also a retention of urea. The appearance of sugar in the urine (observed in many cases) speaks in favour of this opinion.

A greater vulnerability of the tissues, through which the blood poisoned by carbonic oxide pours, may justly be assumed, since it is attested by those cases in which, as in the one communicated by me, extensive gangrene of the skin occurred at places specially exposed to mechanical friction or injury. The observations of Cohnheim on the changes in vessels, which were removed for a time from the influence of normally oxygenated blood, present here, perhaps, more than an inference from analogy.

[1] See Traube, *Gesammelte Abhandlungen*, i. p. 392 et seq.

If we adhere firmly to the fact that the longer duration of the poisoning is favourable to the occurrence of these secondary changes, then the restoration of a poisoned person depends chiefly on the rapidity with which the physician can free his blood from the poisonous gas. It cannot be doubted that a relatively small quantity of quite pure blood greatly accelerates the elimination of the poison.

Transfusion, therefore, in cases of persons poisoned with charcoal vapour must not take the last place—must not be regarded as the last resource—but, on the contrary, must be applied first and before all other measures.

From the action of the freshly injected blood, however, it also directly follows that transfusion alone is not sufficient to free the blood from the poison if the second necessary factor, the oxygen, is not at hand. Artificial respiration after transfusion must therefore be employed in all those cases in which the respiration does not spontaneously convey a sufficient supply of air to the lungs.

Finally, the weakness of the heart, demonstrated by Traube,[1] is a link in the chain of pathological disturbances that must be removed; so much the more, since the extent of the surface of contact between the blood and the air in the lungs, and consequently of the rapidity with which oxygen is absorbed by the blood, depends on the rapidity with which the blood circulates.

With respect to the methods of artificial respiration to be employed, I would always begin with the simple ones—the reflex production of respiratory movements by stimulation of the skin. For this purpose it is easiest, and also most suitable, to apply cold affusions in a warm bath—a proceeding which, even by itself alone, has yielded good results in the treatment of persons poisoned by charcoal fumes. Looked at from a practical point of view, this measure has the great advantage that the application of it may be left to the public, and therefore the physician is not required to remain for a long time constantly beside his patient.

I need scarcely remark that in recommending cold affusions

[1] Loc cit. p. 450.

as a method of promoting artificial respiration I have said nothing against any direct method.

The application of cardiac stimulants, and the form of these which appears to me appropriate, I have already mentioned.

Unfortunately it is often so late before the physician has an opportunity of treating cases of poisoning with carbonic oxide, that there remains small prospect of success. But I believe that a treatment carried out in the different directions which have been discussed gives better prospect of success than a one-sided treatment consisting of transfusion, or of artificial respiration, or of stimulants.

A *previous blood-letting* appears always to be imperative. It is allowable because other red blood-corpuscles take the place of those that are lost by the depletion. Whether, by very rapid formation of carbonic acid from carbonic oxide, a possibly hurtful increase of the former gas may not take place is certainly still an open question; but it is one of so much importance that even on this ground venesection is justified.

There is only very seldom an opportunity in practice of seeing a case of pure *carbonic acid poisoning*; a contemporary deficiency of oxygen must always be present. It will hardly be disputed that a condition which has originated in disease of the respiratory organs or of the heart, such as croup, catarrhal pneumonia, in rare cases also diffuse croupous pneumonia, catarrh with much emphysema, cardiac insufficiency, &c., must not be treated with transfusion. The causes continue; the injected blood is again in a very short space of time charged with carbonic acid, and thus no advantage is to be gained from it.

In cases of suffocation from hanging, perhaps also of drowning, some advantage might rather be expected. The important point would be to raise the greatly lowered excitability of the nerve-centres to such an extent that they may again be rendered capable of exciting spontaneous respiratory movements.

The theoretical justification of this indication is evident. In experiments on animals transfusion has been serviceable; and Eulenburg and Landois have been able fully to confirm the experiments of former investigators. How the case stands with patients remains still to be tried. There are only a few cases known in which transfusion was attempted in still-born children.

In these an injection of about 15 to 30 grms. ($\frac{1}{2}$–1 oz.) of defibrinated blood was made into the umbilical vein, after permitting as much to escape from the umbilical artery. Out of six cases tabulated by Landois only one was successful. There are no experiments on adults recorded. Landois recommends centripetal arterial transfusion in these cases.

In other forms of *poisoning, proceeding from an accumulation of substances normally produced in the body—cholæmia, uræmia*—transfusion is also recommended by some physicians (Eulenburg and Landois). It is always necessary that it should be preceded by a venesection, as part of the injuriously acting material can in this way be eliminated from the circulation. *A priori* there is not much to be said against this indication in itself, at least as regards *cholæmia;* for of course the biliary acids dissolve the red blood-corpuscles, and it is conceivable that the destruction might take place of so many as would be sufficient to make a renewal of them from without desirable. But in the case of the patient that would only happen under conditions which depend on permanent and not on temporary disturbance. In the most favourable case we could only reckon on merely transient improvement, extending, perhaps, only to a few hours. The question whether for such a return a transfusion is to be made is left for consideration in the individual case.

In *uræmia* the case is somewhat different. Direct destruction of the red blood-corpuscles is indeed excluded in all circumstances. It seems necessary to decide—sometimes in the one way, sometimes in the other—the question whether the impairment of the activity of the kidneys is attended with positive injury (formation of carbonate of ammonia), or only with negative injury (accumulation of substances not in themselves injurious, but which disturb diffusion, in the sense in which Voit understands it, e.g. especially urea). Definite indications are wanting; because, at one time, transfusion must be judged according to the principles laid down in cases of poisoning, at another time it must be judged more generally. The question must be asked, whether by temporary increase of the heart's action an increase in the secretion of urine can be effected, or an impending œdema of the brain averted, &c.

As uræmia is distinguished by a certain complexity of symptoms, rather than by a manifestation of any particular organic change, the indication for transfusion cannot be defined with certainty. For the most part, the question turns on continuously active, inaccessible pathological changes. The limit demanded by these is usually quite evident. But it cannot be denied that, under certain circumstances, transfusion may be of some benefit. Experience of its use, it is true, is scanty. In that form of puerperal eclampsia which depends on uræmia there are successes recorded (Lange, Belina [1]). Even in uræmia, in cases of severe kidney disease, transfusion seems to have been, at least, of temporary advantage.[2] It is possible that the acute form of nephritis following scarlatina, diphtheria, &c., when it is accompanied with uræmia, might present better prospects, as all that we have there is only the temporary closure of the renal passages, which may possibly be removed by strong arterial pressure.

The forms of *poisoning* which we attribute to the presence of some germ or ferment which has entered the body from without, but which is capable of multiplying within it (*pyæmia* and *septicæmia* may be mentioned in the first rank), have also been shown to be benefited by transfusion combined with previous depletion. The opinion of the physiologist Panum differs, it is true, very much from that of the surgeon Hueter.

Panum [3] says—

'It has not been remembered that the active poison in these diseases, however people may conceive of it, continues most certainly to be produced and reproduced in the affected organism; and that this occurs, in all probability, not only in the blood, but also outside it in the tissues; and it is evident that no one has formed a clear idea as to the rapidity with which the circulation proceeds, and how small, probably, is the quantity of poisonous material existing in the blood, and carried along with it, at each single moment; and how quickly these small quantities are replaced by other small but constantly following quan-

[1] *Die Transfusion des Blutes u.s.w.*, p. 21 et seq.

[2] Stöhr, 'Transfusion gegen acute Urämie,' *Deutsch. Archiv für klin. Medicin*, vol. viii. 1871, p. 467 et seq.

[3] *Virchow's Archiv*, vol. lxiii. pp. 23, 24 of the separate edition.

tities; and how great their total amount is when they are all reckoned up. The quantity of the poison which in such cases can be eliminated by depletion will, therefore, be exceedingly small in comparison with the amount produced in the course of a day; and, after the whole of the blood has passed a few times through the heart (in the course of a few minutes), the quantity of the poisonous substance present in the blood will probably be just as great as it was before transfusion. I consider it, therefore, an unfortunate misconception of the effect of transfusion combined with depletion, which I once introduced as a subject of discussion, if anyone supposes that it is rationally indicated in such diseases.'

Hueter,[1] who indirectly acknowledges the justice of these statements of Panum when looked at theoretically, refers, on the other hand, to his own experience. He adheres firmly to the belief that a transfusion of 500 grms. (17 ozs.) of 'fever-free' blood decidedly benefits a pyæmic patient for about five days—generally, because the fever abates; locally, because the previously unhealthy surface of the wound, 'after a few hours, shows the formation of healthy pus, and, as a result, begins to granulate.' 'As in many cases of injury the conditions for the further development of the fever can be moderated or arrested in this period, it appears to me to admit of no doubt that the transfusion of fever-free blood in the first stage of serious cases may have the effect of saving life, even if it should require to be repeated once or twice; and certainly, though only in a limited number of cases, may lead to a definite cure.'[2] The statistics, comprising but few cases—in Landois' experience 29 (24 unfavourable, 1 doubtful, and 4 favourable)—would seem to speak more in favour of Panum's opinion. As a rule, the patients under consideration are such as have little prospect of living, and therefore further empirical trials appear permissible.

Landois and Eulenburg have proposed transfusion also in cases of poisoning by *ordinary poisons, not generated within the body*. As the leading fundamental idea, they say,[3] 'the toxic substances,' which exert their injurious influence on

[1] See *Kritisch-antikritische Wanderungen*, p. 161 et seq.
[2] Hueter, *Centralblatt für die medic. Wissenschaften*, 1869, p. 389.
[3] Loc. cit. p. 17 et seq.

the body, act in such a way that at first they are taken up into the blood and carried along with it to those parts in which they make their deleterious influence especially felt. So soon as the poison has passed into the blood its injurious influence, as a rule, is no longer to be effectually combated. But we shall be able to eliminate the injurious influence of the poison if we remove from the body the blood with which the poison is mixed, and in its place introduce normal blood into the vessels. If the poison, as is often the case, is gradually being absorbed, a repeated substitution of normal blood will be necessary so often, indeed, as the threatening symptoms appear to reach their acme. A repeated *washing out*, as it were, of the vascular system by normal blood is required here. From this point of view, 'transfusion with simultaneous depletion must be regarded as a *summum remedium*.'

This view, in my opinion, is not quite so simple as it appears at the first glance. It is necessary first to get some quantitative estimations of its value.

Let us suppose that, to a man of 75 kilogrammes weight, one gramme of poison has been so administered that the whole of it is at one and the same time contained in the blood. As we usually reckon the blood to be $\frac{1}{13}$ of the body weight, the man in question would have 5·769 kilogrammes of blood. There are thus 100 centigrammes of poison contained in 5,770 grammes (5·769 + 0·001 kilos.) of blood. 500 grammes of the poisoned blood are now withdrawn, and in its place 500 grammes of healthy blood injected. The mixture, therefore is as follows:—

Depletion and Subsequent Transfusion of 500 Grammes of Blood	Poison removed from the Vessels	Residue of Poison in the Vessels	Degree of Dilution of Poison
	Grms.	Grms.	
0	0	1·0	$\frac{1}{5770}$
I.	0·0867	0·9133	$\frac{1}{6318}$
II.	0·0791	0·8342	$\frac{1}{6917}$
III.	0·0723	0·7619	$\frac{1}{7573}$
IV.	0·0660	0 6959	$\frac{1}{8292}$
V.	0 0603	0·6356	$\frac{1}{9079}$

This table shows that the washing out of the poison is a peculiar process. Even on the supposition that all the poison

was contained in the blood at the same time, which almost never happens, still further, on the supposition that the quantity under consideration is only one gramme, which, as regards vegetable poisons, is likewise hardly conceivable, such quantities of blood would be necessary for transfusion as are scarcely to be procured. Moreover the necessary quantity of blood can never be precisely defined, for the excretion of the substances taken up into the circulation begins immediately; and besides this they permeate the tissues, mingle with the fluid contained in them, and thus undergo further dilution. We cannot, therefore, at any given time even approximately tell how much poison is present in the blood, and in what degree of concentration it is. The greater the dilution of the poison, so much the larger must be the quantity of blood which should be employed for the purpose of 'washing out.'

The whole idea appears to me on other grounds only doubtfully justified—at all events, it does not hold good in every case. With regard to by far the greatest number of poisons, especially the alkaloids, it is warrantable in the present state of our knowledge to believe that they have their particular locality of action in the central organs, the nerves, and muscles, and often only in a narrowly restricted area, but, at all events, not in the blood, which is a mere means of conveyance for them. Now it is certainly correct, and Ludimar Hermann in his time did not give too great prominence to the fact, that the essential point to be looked at is the strength of the solution of the poison at its seat of action. But this is not materially changed by the transfusion of a small quantity of blood, since we have to conceive of the poison as distributed, after a few minutes, over the juices of the body generally. Whether specific affinities, similar to those met with in chemistry, exist between many poisons and the tissues on which they act—perhaps simple chemical compounds, such as that between carbonic oxide and hæmoglobin—is a question the justice of which cannot be set aside. Depletory transfusion would then appear to be of subordinate importance.

The experiments of Eulenburg and Landois are not very extensive, and, as it appears to me, not very convincing. They have chosen in the case of *morphine* the method of control

experiments, in which two animals, of similar weight and appearance, receive the same poisonous dose; then one is left to itself, and the other undergoes the treatment, the value of which we are desirous of testing. In order to exclude mere accident, which plays a principal part here, where individuality must be regarded as an important factor, the number of experiments must be large. Eulenburg and Landois relate *one* double experiment on the dog with morphine, which is not reported with sufficient exactness to permit of further judgment; the weights are wanting.

With respect to *strychnine* there is only one simple experiment communicated at length—again without statements of weight. The result was fatal, notwithstanding that considerable quantities of fresh blood were injected (29 syringefuls of 16 c. c. or $\frac{1}{2}$ oz. each [1]), and only $\frac{1}{10}$ grain of strychnine was injected subcutaneously.

Also in a second experiment ($\frac{1}{4}$ grain of strychnine administered subcutaneously) a depletory transfusion succeeded in keeping a moderately sized dog alive for only 25 minutes.

These bare facts alone are published.

I am not inclined to believe that they can be considered as affording experimental proof in favour of depletory transfusion as a remedy for poisoning with alkaloids, especially morphine and strychnine.

Quite as scanty are the experiments on animals by Eulenburg and Landois in poisoning with *ether* and *chloroform*. They, as well as later investigators,[2] have not succeeded in restoring animals to life which for a considerable time—above a quarter of an hour—have been inhaling chloroform with an insufficient supply of atmospheric air.

There appears to me to be another point of view worthy of notice: in the first place, as regards poisoning by chloroform and ether, and, in the second place, as regards poisoning by alkaloids.

If death from suffocation ensues after inhalation of chloro-

[1] At the place where this experiment is recorded, only the number of syringefuls is given, but in an earlier page (p. 10) the contents of the syringe are reckoned at half an ounce.

[2] Vide Landois' principal work, p. 127.

form, the real cause must be an accumulation of carbonic acid and a deficiency of oxygen in the blood, produced by the depressing action of the chloroform on the excitability of the respiratory centre. The excitability may be restored by a supply of oxygenated blood, and the respiration will then be capable of removing the chloroform with the carbonic acid. There is therefore an indirect result of poisoning with chloroform, the further action of which extends to a greater retention of the poison, and permits of the simultaneous removal of it, as well as of its resultant action. The same thing may be said of ether, and generally of all anæsthetics inhaled in a gaseous form.

A poison in solution mingled with the blood is eliminated by the secreting organs—the kidneys, the sweat glands, &c.—which in their activity are essentially influenced by the height of the arterial blood pressure. If the pressure within the arteries sinks, then the elimination of the poison is less. Many poisons—for instance, morphine (Binz)—cause a lowering of the arterial pressure, and consequently a longer continued bathing of a given part of the organism with a concentrated solution of the poison. If by depletory transfusion we succeed in raising the arterial pressure, then the elimination will proceed more rapidly, and the remaining quantity of the poison will thus become attenuated as well as by mixture with the blood injected. Under these circumstances the same state of matters will exist in the last instance as in the forms of poisoning just discussed.

If we draw the right inference, then depletory transfusion is a good and well-founded proceeding in cases of poisoning which are accompanied with injury to the red blood-corpuscles, as in poisoning by carbonic oxide and, among others, by chlorate of potash. In cases of poisoning where the blood is not affected, transfusion appears for the present neither empirically nor theoretically to be particularly recommended. It would be going too far were we to deny that it is of any importance; but extensive experience as to an uncertain remedy must be obtained before its value can be estimated. Experiments on man are wanting.

In order to be able fully to estimate the value of transfusion, abundant statistics, containing thousands of cases, are necessary.

By an accumulation of numbers alone is the objection to be set aside that dissimilar cases are compared. The collections of cases made hitherto are not sufficient. In the best among them—that of Landois in his principal work, extending to the end of the year 1874—there are recorded 347 cases of transfusion of human blood into human beings, and 129 cases of animal blood into human beings. These are only a very few of the transfusions that have been made, and the unfavourable terminations among them are far from being always concealed, as is often believed. Esmarch, for instance, before the introduction of the so-called 'bloodless surgery,' was in the habit of defibrinating and injecting into anæmic patients the blood which they had previously lost in the course of a serious operation. Other surgeons did the same—Volkmann and Nussbaum, for instance—and even now many cases, in which Esmarch's method is inapplicable, are treated in the same way. The number of all these cases cannot be small.

How much outward conditions control the success of transfusion—how often it is ineffectual by being 'too late' or 'too small,' &c.—we are taught by the fact that out of 108 cases, where it was performed in flooding following parturition, as recorded by Landois,[1] only 63 proved to be successful: here full warrantable justification for transfusion cannot be doubted.

If it is justifiable to desire sufficient statistics, it is quite as justifiable, on the other hand, to characterise the material hitherto existing as insufficient.

The question remains, Do *general contraindications* exist which forbid the application of transfusion even in a case in itself entirely suitable?

Were the conclusions of Köhler correct, then the 'ferment poisoning' which follows the introduction of defibrinated blood might be characterised as so preponderating an objection that, at most, transfusion from the artery of one into the vein of another individual ought only to be performed. But, to enforce these conclusions, Köhler's whole theory must be better supported than it actually is. Single observations, such as those communicated by Köhler himself from Bergmann's

[1] Loc. cit. p. 328.

clinic, and those lately mentioned by Casse,[1] go no further than to increase the number of unfavourable cases, which, occurring as they do in every other operation, also occur in transfusion. The overpowering majority of experiments on animals and of the observations on human beings stand in direct opposition to these.

Panum most emphatically points out that 'a great weakening of the nervous system, and specially of the nerves of the heart, giving cause to fear the occurrence of cardiac paralysis during the operation,' is to be regarded as a contraindication.

A number of deaths during transfusion—and the number known, at least, is not large—may have occurred from this cause. I consider it as an established fact that the uniform and slow transfusion of blood, as it can be accomplished by the aid of the burette, is capable of very much diminishing this danger. Besides, before beginning the operation, the physician will do his best, in view of the threatened paralysis of the heart, or, more correctly, the well-marked weakness of the heart, to increase the activity of the heart; and means are at hand for this end. I cannot acknowledge this as an unconditional contraindication, otherwise transfusion would be restricted in the very domain in which its greatest usefulness lies—that of acute anæmia. Here no general rules can be given; it depends on the character and temperament of the physician on whom it devolves to answer the question, whether a last trial is to be made or whether the matter is to be left to itself: the energetic will act, the cautious will refrain. The same remark is applicable whenever, beyond the bounds of rational indications in the stricter sense of the word, therapeutic experiments come to be considered. 'If blood *suited* to transfusion were easily and abundantly to be had, then one might be induced to perform this operation frequently as a symptomatic remedy:' this is an admission made by Panum, who elsewhere comes forward as the champion of the limitation of transfusion to the narrowest indications. Only, one must not transfuse at random, as has been done. What could a man have imagined when he attempted to cure 'epilepsy, with weakness of mind,' by an ounce of defibrinated blood (Polli, 1851)?

[1] See *Centralblatt für Chirurgie*, year 1880, No. 8, p. 117.

Certainly one contraindication may be put down as entirely unconditional: *if, in a given case, no reason, which is scientifically supportable, can be adduced for the performance of transfusion as a therapeutic measure, it ought not to be done.* This self-evident fundamental rule, applicable to every other operation, must have been forgotten by many when practising transfusion.

EPIDERMIC, ENDERMIC, AND HYPODERMIC ADMINISTRATION OF MEDICINES.

BY

PROF. A. EULENBURG,

OF GREIFSWALD.

TRANSLATED BY

MATTHEW HAY, M.D.,

PROFESSOR OF MEDICAL JURISPRUDENCE IN THE UNIVERSITY OF ABERDEEN.

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EPIDERMIC ADMINISTRATION OF MEDICINES.

(EPIDERMIC METHODS IN THEIR MORE RESTRICTED SENSE.)

By this we understand those methods of medicinal administration *in which the remedy is brought into contact with the uninjured epidermis or outer layer of the skin, for the purpose of effecting the absorption of the remedy, and thereby permitting the medicine applied to produce its general action on the system.*

The application of remedies to the epidermis, whether with the object of procuring a purely local effect, or for the purpose of producing by absorption an action on the whole system, can be made in various ways, by means of very many various pharmaceutical forms, differing in consistency, method of preparation, &c. As is well known there are a large number of pharmaceutical preparations which are especially adapted for external or epidermic application. Among the dry or solid preparations, may be mentioned caustic pencils, caustic pastes, dusting powders, wash powders, soaps, and dry poultices; among semifluid, soft or viscid preparations—moist poultices, liniments, salves, cerates, and plasters; among fluid preparations—baths, lotions, wet compresses, and fomentations; among gaseous preparations—vapour baths, steam baths, and fumigations. Details of the making of these various pharmaceutic preparations, and of their prescription and application, will be found in the handbooks of pharmacy, prescribing, and dispensing, and partly also in works on hydrotherapeutics and balneotherapeutics. Here we have to deal with all these therapeutic methods only in so far *as they can be made serviceable for the absorption of medicines, or at least in so far as the possibility of absorption has been contemplated.*

In order to exclude misunderstanding, let it be expressly

mentioned that local action and general action are not to be understood in such a sense as to imply that the latter can only be effected by the method of absorption *when remedies are applied externally*, and that thus general action and action by absorption must be regarded as essentially identical. This is by no means the case in the external application of remedies; on the contrary, even when absorption is entirely excluded, and the medicine exerts a purely primary local action, nevertheless it is possible to remove secondarily very varying and intense general symptoms, by means, for instance, of a reflex effect on the heart, vascular tonicity, respiration, temperature, tissue metamorphosis, &c. This is so much the case with baths that, according to the views prevailing in the present day, we regard the action of all, even of medicated baths, as being due to the mechanical, chemical, and thermal stimulation of the skin in its manifold gradations, and to the secondary effects which are reflexly produced. The local as distinguished from the general action of a medicine applied epidermically can, therefore, only refer to the effects produced locally, and to the general effects due to the absorbed drug, as such; or to the local, inclusive of the reflex, effects, and to those caused by absorption.

Accordingly the first and most important question in estimating the value of the epidermic application of remedies and its special method is undoubtedly this: *With this procedure can there be any question at all of an absorption through the (normal and uninjured) epidermis; and if so, under what particular circumstances, and with what form of the medicine, and modifications of the method of application, can the absorption be promoted or made possible?*

This question, of course, could arise only at a time when the great aim is to approximate more to an accurate understanding of pharmacological action, and to define scientifically its fundamental conditions by means of experiments and clinical investigations. We must not therefore wonder that the literature of this subject is for the most part of comparatively modern date, and that the question itself is not even yet fully and finally solved in a satisfactory way. Formerly, they employed the epidermic medicinal forms, hallowed by age and tradition, of baths, salves, poultices, &c., without troubling

themselves at all about the manner of their action, as they had unquestioning faith in the general action produced by the absorption of medicines employed in such a way. Yet, in the last respect, doubts more and more well-founded must gradually rise when more particular observation is directed to the structure of the outer skin; and we may regard as evidence of these doubts, the various proposals made since the beginning of the present century to promote and assist by certain procedures the action of externally applied medicaments in the treatment of internal diseases. To these belongs the proposal made by Brera in his 'Anatripsology' (1800) 'to act on the body by inunction with animal juices and various substances which are usually administered internally,' a proposal which a few years later was accepted by Chrestien in the form of the 'iatroliptic method,' or in that of 'cispnoic medicine.' The method of treating internal diseases was, to employ as an inunction externally the suitable remedies, mixed with animal secretions, saliva, gastric juice, pancreatic juice, and bile, under the belief that to a certain extent they could in this way be conveyed in a digested form to the organism. Others justly maintained that inunction of portions of the skin, where it is especially thin and vascular, or still better mucous membranes, must facilitate and promote absorption. This idea gave rise to Wardrop's proposal of inunction of the tongue and gums, Cirillo's recommendation of the soles of the feet, Forgét's suggestion of inunction of the axilla, which is covered with thin skin (*maschaliatry*, from μασχάλη, the axilla). From the same source proceed also the experiments made by Klencke and Hassenstein on the application of electricity to facilitate the penetration of drugs into the body through the skin (galvanic applications, chemico-electro-therapeutics), of the later and somewhat more successful revival of which we shall afterwards speak.

Latterly the attention of balneologists has been largely turned to the question of cuticular absorption, which is of very great interest as regards the theory and use of the various forms of baths, particularly mineral and other medicinal baths. Here also, in earlier times, there existed no doubt as to the permeability of the skin to the substances dissolved in the

bath; on the contrary, it was on this very permeability that the specific action of the various mineral baths (chalybeate, alkaline, saline, and sulphurous baths, &c.) and their therapeutic indications and contra-indications were everywhere believed to depend. It is well known that the balneologists of the present day, or at least by far the greatest part of them, have more or less entirely renounced this way of thinking, and, on the contrary, do homage to an idea of the action of baths which entirely excludes all consideration of absorption as an integral factor. J. Braune is perhaps the first who, in his systematic text-book of balneotherapeutics, gave expression most energetically to this view. But the incredulity of the present day may possibly have no better foundation than the superstition or credulity of former times, and in fact he is condemned as going too far even by many eminent balneologists. Let us therefore enter the arena ourselves, and at least take a rapid survey of the empiric and experimental demonstration of the existence or absence of cutaneous absorption from baths.

In doing this we have specially to distinguish between the absorption of *gases* contained in the water, of the *water* itself, and of the *solid substances* (salts, &c.) dissolved in the bath.

1. The possibility of the *absorption* of *gases* and *vapours* through the uninjured cuticle has, properly speaking, never at any time been seriously called in question; but it has, on the contrary, been expressly acknowledged by the admission of a cutaneous respiration, both in warm-blooded animals and in man. Later experiments have proved (Regnauld and Reiset) that an absorption of oxygen in fact does take place by the skin, which approximates to, or indeed almost equals, the volume of carbonic acid exhaled with the sweat, and that thus a regular interchange of gases, a respiratory activity of the skin—inconsiderable, it is true, in comparison with the interchange of gases in the lungs—takes place. In accordance with this, stand the numerous pathological and experimental observations which relate to the appearance of poisonous symptoms after the absorption of toxic gases (carbonic acid, sulphuretted hydrogen) and vapours by the uninjured skin, as also the chemical proof of the presence in the body of certain of these gases (sulphuretted hydrogen), and, still further, those observations which

prove the permeability to vapours and gases of a portion of the epidermis which has been removed from the body (experiments of Abernethy, Collard de Martigny, Lebküchner, Chaussier, Krause, Gerlach, Herpin, and others). It may indeed be objected to the last of these experiments that the permeability of the dead excised epidermis appears to be greater than that of the living, so far as many substances are concerned ; on the other hand, in the absorption of many gases and vapours, there must be taken into consideration their chemical action and their stimulating effect on the glands of the skin (*vide* under). In any case there are positive indications enough to authorise us in regarding as not impossible a partial absorption at least of the different gases existing in mineral baths (carbonic acid, sulphuretted hydrogen). With regard to *carbonic acid*, according to the experience got from dogs' grottoes, carbonic acid baths, &c., its absorption by the uninjured skin is probable enough to justify founding on this experience, at any rate to a certain extent, the therapeutic use of gaseous baths and of warm baths rich in carbonic acid. Herpin mentions that he has observed a darker colouring of the venous blood after a carbonic acid bath of several hours' duration. A considerable measure of absorption appears to take place only under strong pressure of the gas ; on the other hand, in the use of baths rich in gas the strong contraction of the cutaneous vessels which takes place prevents, we may suppose, a great absorption of carbonic acid, so that in the last instance the action of mineral baths containing carbonic acid is probably dependent much less on absorption than on local stimulation of the sensory nerves of the skin and their reflex effects on nutrition, tissue metamorphosis, &c. That *sulphuretted hydrogen*, either by itself or dissolved in water, is absorbed by the skin, and may act poisonously and even lethally, has been proved beyond a doubt by the experiments on animals of Lebküchner, Chaussier, Falk, and others. Whether, however, the effects of sulphurous baths, as is maintained by many, are partly produced by the absorption of the gases dissolved in the bath, remains at least extremely questionable, when we consider the very small quantity of sulphuretted hydrogen usually contained in sulphurous waters and the absence of the characteristic symptoms of its toxic action after the use of these

baths. Similar assertions might be made regarding the quantities of carbonic acid, sulphuretted hydrogen, carburetted hydrogen, nitrogen, ammonia, &c., contained in the Turkish bath. Probably in all these cases also the temperature of the bath plays an important part, as appears from the interesting experiments of Brémond on medicated (iodide of potassium) vapour baths, according to which absorption usually only takes place at 38° C., or just about 1° above the temperature of the body, and is in direct proportion to the temperature and duration of the bath and to the quantity of iodide of potassium contained in it.

2. Whilst the absorption of gaseous substances by the skin may be considered as a firmly established fact, though not exactly of great importance for therapeutic practice, the absorption of *water*, on the other hand, has until recently been the subject of keen controversy, and has been decided in an overpowering negative. An attempt to prove the absorption of water by the skin was made by comparing the weight of the body before and after the bath; in many cases an increase of weight was reported, of little consequence as a general rule, but at times amounting to several pounds, frequently too accompanied by increased diuresis (Young, Collard de Martigny, Wetzler, Falconer, Kathlor, Madden, Berthold, Krause, Eichberg, Valentin, Duriau, Willemin, and others). Berthold estimates the increase of weight, after a bath of 26° C., lasting one hour, at 60 grms. (2 oz.); Duriau, after a bath of 25° C., at 35 to 75 grms. within 75 minutes. To these weight-experiments, however, were opposed as many others with a decided negative result—in fact, with the result of a small decrease in the weight of the body, caused by increased excretion from the skin and lungs. It was, moreover, justly alleged against these pretended positive results of weighing that at the same time no account was taken of the temporary variations in the loss of weight occurring through the skin and lungs, and that even a small increase of weight may be attributed to nothing more than the greater or less soaking and swelling up of the epidermis from imbibition in a prolonged bath (Currie, Séguin, Kletzinsky, Falk, Poulet, Lehmann, Hébert, Thomson, and others). The very precise experiments of Duriau prove that the temperature of the bath plays an important part in changes of weight,

evidently from its influencing the perspiration of the skin, which only attains a considerable activity at about 32° C. Baths below this temperature may therefore produce an increase of weight; baths of a higher temperature (35° to 45° C.) may cause, on the contrary, a decrease in weight, even amounting to 600 grms. (20 oz.) in ten minutes. Quite as contradictory were the results obtained by comparing the weight of the water in the bath before and after the bath (partial or complete) had been used. In doing this sources of error, arising from evaporation and variation of temperature, add of course to the difficulties already presented in obtaining precise weighing. The latest experiments, made with all necessary precautions, have returned results more and more unfavourable to the theory of cutaneous absorption. We must not omit to take into consideration the recently published results obtained by R. Fleischer. His investigations were made on the arm, by means of Mosso's plethysmograph, or of a bell glass, which was filled with water under a tolerably high pressure from an elevated reservoir; the air-tight glass was placed on a particular part of the skin. The plethysmograph as well as the bell glass was connected with a thin, graduated, vertical tube, which indicated with great precision any decrease of the water. If variations due to evaporation and temperature were avoided, *then no demonstrable change in the volume of the water ever appeared, even though the experiment lasted for several hours.* (In a similar experiment alcohol seemed to be quite as incapable of being absorbed by the skin as water; the volume of the alcohol was in the air-tight glass altered by evaporation, exactly as in a second and control glass, which was not in contact with the skin. The case is, of course, different with fluids, which, like chloroform, irritate and excoriate the skin.)

3. The most numerous, and in their results the most important, investigations refer to the absorption of *solid substances* dissolved in the bath. These were made to act in the form of prolonged partial or full baths, and the attempt was made to demonstrate them or their derivatives either in the skin itself or in the excretions of the organism, especially in the urine, or even to bring forward proof of their absorption by the occurrence of symptoms of their action. Clemens, among

others, was the first to test this, making use of local baths of common salt (arm baths); and, long after the bath, he succeeded in recovering salt from the skin, which had been previously carefully cleansed and washed. To this and similar experiments, it is true, the objection may be made that, apart from any other sources of error, the whole effect depends on a simple mechanical retention of the salt by imbibition in the swollen and macerated epidermis; at all events the occurrence of absorption by the skin is not actually proved by these experiments. In this respect the experiments which relate to the demonstration of the constituents of the bath in the urine, &c., lead us further, though here also doubts and erroneous interpretations frequently creep in. Thus, for instance, after the prolonged use of alkaline baths, a neutral or even an alkaline reaction of the previously acid urine has been found, and from this the absorption of alkali has been inferred (Spengler, Ditterich, Chevalier, D'Arcet, Petit, and others), whilst, on the other hand, control experiments undertaken by later investigators have shown that prolonged baths of any kind, even such as contain mineral acids, regularly lower the acidity of the urine (Duriau, Zülzer). Very contradictory also are the results as regards various substances which are either easily to be found in the urine as such, or are very distinctly characterised by their action (iodide of potassium, ferrocyanide of potassium, salts of iron, arsenic, and mercury, rhubarb, turmeric; salicylic acid, sulphindigotic acid; belladonna, digitalis, &c.) Numerous investigators attained by the use of these methods to positive results (Bradner, Stuart, Westrumb, Lebküchner, Wedekind, Seiler, Ficinus, Bonfils, Ditterich, Ahlefeld, Willemin, Delore, Henry, Rosenthal, Bolze, Waller, Hoffmann, Brémond). Many others, on the contrary, obtained entirely negative results (for instance, Kletzinsky, Arneth, Zieckauer, Lehmann, Homolle, Hébert, Reveil, Benecke, Duriau, Parissot, Thomson, Brane, Zülzer, Teissier, Demarquay, Röhrig, and recently Fleischer). It, however, cannot well be doubted that in this case the negative results are in general more convincing than the great majority of the positive. Apart from other sources of error, which in many forms are attached especially to the older experiments, it must be particularly taken into consideration that in com-

plete baths, sitz baths, &c., very small quantities of substances can be absorbed, on the one hand, through injured portions of the skin deprived of their epidermis, and, on the other hand, through the exposed mucous membranes (præputial, vaginal, and rectal), and thus produce their action, and even appear in the urine. The latter, as Demarquay has shown, is true in reference to iodide of potassium. On the other hand, in experiments made with this drug, although it was applied with the observance of all necessary precautions for several hours in the form of concentrated local baths (arm baths) or fomentations, not even a trace of iodine could be detected in the urine. The same thing holds good of ferrocyanide of potassium and other substances, whose presence is easily detected in the urine. Parissot, who experimented on adults and children with more than a hundred medicated baths of 28° to 30° C., could not in a single case detect traces of the dissolved substances in the saliva or urine, and still less any toxic action of the substances, even when very concentrated solutions of belladonna, digitalis, &c., were used. Fleischer's experiments with 1·2 to 1·3 per cent. solutions of iodide of potassium, as well as with solutions of salicylic acid and sulphindigotate of soda, produced entirely negative results. That strychnine, hydrocyanic acid, and other extremely active poisons may even in concentrated solution remain quite harmlessly in contact with the uninjured skin has already been long known (Magendie); it was also lately confirmed with regard to strychnine in animals by H. Munk. Also Teissier and others, when all necessary precautions were taken, never perceived the smallest signs of absorption after very concentrated baths of corrosive sublimate and arsenic. Such, however, may appear to a small extent if, after the removal of the bath, a little water with the drug in solution still adheres to the skin, evaporates on it, and the residual solid, by its irritating action on the glands of the skin, increases their excitability, or chemically affects the skin (vide below). Such an absorption, however, must be regarded as a secondary process, not caused by the baths themselves, but by the local irritative action of the solids derived from the baths. Its occurrence, apart from the differences caused by individual peculiarities of the skin, will be in general so much the easier,

the more concentrated the solutions are which are used in the bath, or the richer it is in substances which are capable of stimulating or acting chemically on the cuticle.

Here also come in experiments which have been made by earlier and later investigators in reference to the diffusion of saline solutions, &c., through excised and isolated portions of the cuticle—removed by the action of vesicants. Krause found in experiments with numerous substances, especially common salt, nitrate of potash, chromate of potash, cyanide and ferrocyanide of potassium, sulphate of copper, acetate of lead, perchloride of iron, as also with sugar, gum, and albumen, that aqueous solutions of these, even after they had been allowed to act for several days, do not penetrate the isolated epidermis; but, on the contrary, it showed itself permeable to concentrated solutions of acids, alkalies, and nitrate of silver (substances, therefore, which have a corrosive action). Zülzer also obtained entirely negative results from his experiments with excised epidermis, which had been isolated by a vesicant. Moreover several observers, and very lately Fleischer, found that the dead skin is more penetrable by different fluids than the living one. From all this it may be maintained, with tolerable certainty, that the epidermis, in a normal uninjured state, is generally impermeable to fluids, or substances dissolved in fluids, and an absorption by it therefore does not take place. Nor does absorption through the glands opening on the surface of the skin appear to take place to any considerable extent from baths that are not too prolonged, perhaps because the sebaceous secretion obstructing the mouths of the glands prevents it under ordinary circumstances. Individual and local differences, it is true, may in given cases produce deviations from the general rule and lead to absorption—e.g. in young persons or females, through thin, tender portions of the skin, rich in sweat glands; in great turgescence and great hyperæmia of the skin, &c. Further, when the bath has continued for an unusually long time considerable absorption may take place, probably from the ultimate removal by solution of the glandular secretion, as, for instance, appears to be proved by Colin's experiment, who, after five hours' application of a solution of cyanide of potassium to the dorso-lumbar region of a

horse, succeeded in poisoning the animal. There is an essential difference between cutaneous absorption from baths and that which takes place *when certain forms of epidermic application are employed, in which the factors favourable to absorption are taken advantage of to a much greater extent.* These factors consist above all in an increased activity of the cutaneous glands, in the removal or solution of the secretion obstructing the mouths of the glands, in the greater turgescence and vascularity of the skin, and finally in the chemically and mechanically altered condition of the epidermis, by means of which an increase of its permeability is produced in the parts not intersected by glands and hair follicles. Particularly effective, therefore, will be the action of such drugs and such forms of application as throw the glands into increased activity by prolonged local stimulation (thermal, mechanical, or chemical), by a higher degree of warmth, by friction, pressure, &c.—or such as dissolve and remove the obstructing sebaceous secretion—or produce an increase of the blood and lymph in the skin, whether by a direct or reflex action on the blood and lymph vessels—or, finally, considerably change the structure of the cuticle in a mechanico-chemical way. The more these various factors are made to co-operate with the respective drugs and their pharmaceutical forms, so much the more certainly will we have, as the total result of the procedure made use of in a given case, a permeation of the cuticle (whether through the glands and hair follicles alone or also through the gland-free interstices), and a penetration into the deeper layers of the skin, and, finally, an absorption of the medicines applied.

Absorption is, therefore, essentially promoted, when the substances to be absorbed are mixed with fluids that stimulate the skin, or also at the same time dissolve more or less completely the sebaceous secretion—e.g. alcohol, ether, chloroform, ethereal oils, &c. ; that is, when the substances applied are dissolved in such fluids. But even solutions of soap—which soften and dissolve the horny layers of the epidermis by means of free alkali or basic salts, and which at the same time, by combining with the fatty acids, chemically alter the cutaneous secretion—as also fats, fatty oils, and glycerine, perhaps in virtue of

their emulsifying qualities or their tendency to adhere to the epidermis, may considerably promote the permeability of the skin and the diffusion of many substances through it. Accordingly it need not cause surprise if substances, which, as a rule, cannot be absorbed from the bath, are more easily absorbed when they are applied epidermically in the form of soaps, spirituous liniments, ointments, cerates, stimulating (resinous) plasters, &c.; but especially so when there is added the effect of mechanical stimulation, pressure, and friction, as obtained by means of *inunction*, and when there is a very long continuance of the application. That under such circumstances absorption may take place to a considerable and even unexpected extent, has long ago been empirically established by numerous observations on the therapeutic and toxic effects of drugs so applied. Inunctions of mercurial preparations, in the form of ointments (mercurial ointments), have, by their therapeutic activity and by the appearance of symptoms of mercurialism, particularly furnished apparently irrefragable proof of this absorption; though even here, with the usual methods of application, absorption by the mouth and nose from an atmosphere containing mercurial vapours can by no means be considered as excluded. Strictly speaking, therefore, even observations such as those of Vidal, Anderseck, and Hamburger on poisoning with mercury after inunction of it in the form of ointment, for the purpose of cutaneous absorption, are not entirely convincing. In this respect observations relating to the manifestation of poisonous alkaloidal action after epidermic application of preparations of opium or belladonna, in the form of liniments, ointments, plasters, &c., are of much greater importance. Thus Hérard saw opium poisoning follow from an opium plaster on the temporal region; Morgan twice saw belladonna poisoning ensue from the application of belladonna plasters in sciatica; and Jenner saw belladonna poisoning take place in the same way. I myself have several times seen symptoms of the action of atropine (mydriasis, dryness of the mouth and throat, &c.) after inunction of ointment of belladonna on the temples, especially in females and in individuals sensitive to the action of medicines. Many substances, even such as strongly stimulate the skin, appear, on the other

hand, not to be absorbed by inunction, or at least to produce no marked general symptoms; as, for instance, croton oil, according to Andral and Marchand. The experimental investigations of Waller, Delore, Parissot, Zülzer, Scoutetten, Neumann, Brémond, Fleischer, and others entirely agree with the results of empirics. Parissot, for instance, found that after an inunction on the temples of 0·005 gramme of atropine in 20 c.cm. of chloroform, dilatation of the pupils ensued in 5 minutes; but that after an inunction of a similarly strong alcoholic solution it took place in 30 minutes. Waller had, even at an earlier date, got the same results. It is well known that, after painting a part of the body with tincture of iodine, the iodine can frequently be detected in the urine; and the same holds good after inunction with ointment of iodine or oil of iodine.

Absorption in these cases, as may be seen especially in the instance of the more solid particles suspended in liniments or ointments, as those of mercury, &c., takes place in such a way as that these particles enter into the open mouths of the cutaneous glands and hair follicles, and are thence gradually conveyed into the deep layers of the skin, from which their absorption most probably takes place, mainly with the help of the lymph vessels of the skin. Thus Zülzer, after inunction of mercurial ointment or ointment of iodide of lead—never, however, after simply laying it on—found the glandular ducts, and partially also the root sheaths of the hairs, filled with particles of mercury and iodide of lead. Neumann, too, saw globules of mercury penetrate into the hair follicle, even down to the bulb, and into the open mouths of the sebaceous glands and the upper part of the sweat glands. Fleischer, after inunction of blue ointment or of oleate of mercury,[1] could follow, both in men and animals, the globules of mercury by means of the microscope into the uppermost layers of the epidermis; that, however, an absorption actually took place was proved by this, that after an inunction of about 1·5 gramme of oleate of mercury on the arms and careful protection of the nose and mouth from vapours of mercury by bandaging the place of the application for 16 hours, mercury was detected in the urine.

[1] Solution of mercuric oxide in oleic acid. Vide Marshall, *Lancet*, March 25, 1872, p. 709.

Certainly with most substances absorption in this way is a minimal and extremely precarious one. According to Fleischer, inunctions of ointments of iodide of potassium, veratrine, morphine, quinine, were never followed by the passage of these drugs into the urine when every possibility of an absorption in any other way than by the skin was distinctly excluded. Only after inunctions of salicylic acid and salicylate of soda, in the form of ointment, were there found, in isolated cases, traces of the drug in the urine, the existence of which, however, Fleischer regards as still doubtful on account of the irregularity in the results obtained. Here we may again refer to the experiments of Brémond, already mentioned, with vapour baths containing iodide of potassium. Whilst, in general, absorption took place only at a temperature of 38° C., on the other hand, by a previous use of vapour baths along with washing with soap and energetic friction, the iodide of potassium was absorbed at a temperature of 34° to 36°, and could be recognised in the urine. Its elimination by the urine began about 2 hours after the bath, and as a rule it was entirely completed 24 hours afterwards. (In these experiments the steam held the iodide of potassium in mechanical suspension; the head of the patient was protected outside of the bath, so that the possibility of absorption through the respiratory passages was excluded.)

If we now review the results contained in the foregoing pages, we may draw the following conclusions with regard to epidermic methods of application of remedies:—

1. *The uninjured human epidermis is undoubtedly permeable to gaseous substances, such as carbonic acid, sulphuretted hydrogen, &c.; on the contrary, apart from possible absorption through the cutaneous glands, it is entirely impermeable to fluids, and to solids, or to substances dissolved in fluids, which do not act mechanically or chemically on the horny layers of the cuticle.* Absorption through the application of dry or moist poultices, and local or general baths, with the epidermis uninjured and unaltered, has as yet been by no means actually proved.

2. *Every absorption of fluid and solid substances that takes place through an uninjured, unaltered epidermis*

appears to be brought about solely by means of the cutaneous glands (the sebaceous and sweat glands, and the hair follicles). It results in particular from the penetrating of the dissolved or solid substances into the mouths of the glands, the ducts of the sweat glands, and the root sheaths of the hairs, whence they are conveyed into the blood by means of the blood and lymph vessels.

3. *In order to promote the penetration of dissolved or solid substances into the glands and hair follicles, and their further absorption, the substances must be applied in such a form that they increase the activity of the cutaneous glands by mechanical, chemical, or thermal stimulation, or effect simultaneously the solution and removal of the obstructing secretion.* These are both brought about by mixing the medicines intended for absorption with stimulating fluids or other substances used as excipients (such as alcohol, ether, chloroform, ethereal oils, resins, soaps, &c.), also with steam, as well as by inunction of the remedy under an increased temperature or heavy pressure.

4. *By the use of stimulating poultices and baths, especially vapour baths, still more, however, by stimulating inunctions (liniments, ointments) and plasters, an absorption of the active constituents may take place through the skin to a greater or less extent.* Besides the mode of the application of the remedy, the idiosyncrasy of the individual, the locality, thickness, turgescence, vascularity of the skin, &c., are of manifest importance. It is true, however, that the intensity of the absorption attained in this way is very small; the result is extremely restricted and insignificant in proportion to the quantity of the drug applied.

The method of the epidermic application of medicines, therefore, so far as it relates to the bringing about of the effects of absorption, may be regarded as being rationally justified in exceptional cases only.

By way of appendix two other methods of epidermic application of remedies may here find mention; they have been proposed very lately, and in them, besides the factors already spoken of, others which have not hitherto attained any practical importance come into co-operation. These are the so-called *aquapuncture* and the *electro-chemical therapeutical* methods.

(Under the last-named we include the experiments on the electrolytic conduction of iodine and the cataphoric action of medicines.)

AQUAPUNCTURE.

The object of aquapuncture, invented by Matthieu, is to drive a fluid—water—in a fine stream through the uninjured skin by means of strong pressure. The fluid is placed in a syringe, of the capacity of several grammes, provided with a very fine cannula, which is held at a distance of about 1 cm. ($\frac{1}{3}$ inch) from the portion of skin to be acted on. A simple pressure on the piston of the syringe suffices to drive the fluid through the skin and into the subcutaneous tissue, so that in the latter there is formed a small whitish swelling, which sometimes contains a drop of blood in its centre. The pain at first is tolerably smart, but soon ceases, and the swelling goes away in 15 to 20 minutes, so that only the trace of a small capillary puncture remains behind. According to the reports of Mallez, Sée, and Guéneau de Mussy, the operation is said to have proved useful, particularly in painful affections—myalgia, neuralgia, &c. I have seen Matthieu's instrument in use, and have also several times used it myself with water or a solution of morphine. I can, however, see in it nothing but a somewhat worthless plaything, quite superfluous at all events as an addition to the hypodermic method.

ELECTRO-CHEMICAL METHODS. ELECTROLYTIC CONDUCTION OF IODINE AND CATAPHORIC METHOD.

Experiments on the electrolytic conduction of medicines through animal tissues appear to have been made even in the last century, by Priestley and others (1767). They were, however, soon forgotten, but were again taken up in 1845 by Klencke, in 1853 by Hassenstein, and by Clemens in 1860. The object was to convey drugs from the epidermis into the body by means of the constant galvanic stream. Hassenstein characterised this procedure as *electro-chemical therapeutics.* One peculiar application of this method, which made a great noise at the time, was the proposal, emanating from Beer in Vienna in 1869, of the 'electrolytic conduction of iodine.' The

permeability of the animal tissues was to be utilised for the purpose of conveying iodine through them from the negative to the positive pole, and by this means to drive a current of iodine, for therapeutic purposes, through certain parts of the body; whereby, whilst obtaining a strong local effect, the general action of the iodine would be entirely avoided. Experiments made by myself, and by Brückner, Benedikt, Ultzmann, Fieber, and Ossikowski have decidedly proved the erroneousness of these efforts and the impossibility of attaining in this way the local effect assumed by Beer, particularly as the resistance of the skin is much too great, and as it is impracticable to conduct the iodine to great depths through complex animal tissues. Besides this, the existence of the circulation alone presents an insuperable obstacle to the penetration of particular portions of the body or of the limbs, as the electrolytically liberated iodine must necessarily be again absorbed in its course and conveyed into the circulation. On the other hand, the investigations lately made by H. Munk on the galvanic introduction of different fluids into the uninjured human and animal organism deserve more serious attention. Munk justly dwells on the failure of former efforts, in which almost always only the electrolytic, but not the *cataphoric*, action was taken into consideration, although conditions very favourable for the latter are present in the narrowness of the pores of the animal body. Of course it is only a general action as brought about by absorption that is here considered, not a local action in the sense intended by Beer. In order to procure a sufficient cataphoric effect the drug must be brought into contact *with the positive electrode, or with both electrodes*; and a tolerably strong current, obtained from 10 to 18 of Grove's elements, is passed for a period of 15 to 45 minutes, the direction of the current being changed from time to time. It is highly advisable to rub the drug with the clay points of the non-polarisable electrodes of Du Bois Reymond. In this way, when experimenting on rabbits, Munk could, by the application of a concentrated aqueous solution of strychnine, produce in 10 to 15 minutes increase of the reflex excitability, in 20 to 25 minutes violent general tetanus, and in 45 minutes of continuous application he could cause death. In man, after the application of concentrated solutions of sulphate

of quinine or iodide of potassium, the quinine could be detected in the urine of the next twelve hours, and the iodine could be detected thirty-six minutes after the beginning of the experiment, but in greatest quantity after the lapse of 5 to 6 hours. The epidermis never presented any appearance of injury. The action, as Munk maintains, may, for therapeutic purposes, be accelerated and increased by enlargement of the surface of contact as well as by the use of several pairs of electrodes one after another. The general action on the body effected in this way may have this advantage over that obtained by other methods, that it takes place gradually with very slow increase; moreover, after the current has ceased to flow, the action of the drug may continue to increase, in consequence of the absorption of the substances left in the skin, so long as the absorption exceeds in rapidity the elimination of the substances. (Reports on the use of Munk's method for therapeutic purposes do not, so far as I know, exist.)

INTRACUTANEOUS OR ENDERMIC ADMINISTRATION OF MEDICINES.

From what has been said with regard to the epidermic administration of remedies, it is evident that it is mainly the epidermic layers of the skin which impede and prevent the penetration and absorption of fluid and solid drugs; and that, on the other hand, gradual maceration of these epidermic layers, as well as various chemical alterations of them, facilitate cutaneous absorption in a high degree. So also we see that fluid and finely divided solid drugs are more easily absorbed, when once they have entered the glands and hair follicles that pass through the epidermis, and have been carried into the deeper layers of the skin. These facts make it highly probable that *the corium, when it is exposed and deprived of the epidermis, is, like mucous membrane, in a considerable degree fitted for the absorption of fluid and solid drugs which are brought into immediate contact with it, and that also when, without previous removal of the epidermis, a direct introduction of the drugs into the deeper layers of the cutis is effected, the absorption of the medicines administered must necessarily*

follow. We may characterise all such procedures, in contra-distinction to the epidermic method, as the *endermic* or *intra-cutaneous administration of remedies.* Those methods in which the drug, in either a fluid or a solid form, is applied directly to the cutis, previously exposed by removal of the epidermis, constitute the endermic method in its narrower sense; but we also have *medicinal inoculation* and *dry injection* or *implantation*, in which the drug is introduced by a fine puncture into the deeper layers of the cutis, and to a certain extent also into the subcutaneous tissue, without removal of the epidermis. Both forms of endermic administration pass, however, as we shall see, into one another by various modifications.

Endermic Methods in their More Restricted Sense.

In order to bring fluid or solid drugs into direct contact with the exposed cutis, *such portions of the skin* may be used for the application of the drug *as have suffered a breach of their continuity, whether produced accidentally or artificially, as wounds and ulcers.* Pathological and clinical experience teaches us that from the surfaces of wounds or ulcers an unintended absorption of the medicines applied for local therapeutic purposes may easily take place. By way of illustration, we need only call to mind the occurrence of carbolic acid poisoning, and the appearance of the acid or its derivatives in the urine, when it has been used in the antiseptic treatment of wounds. To a certain extent the methods adopted in experimental physiology in the last century, and still more in the present one, for the investigation of the action of drugs and poisons on animals were of the nature of endermic methods (vide Inoculation). With reference to absorption from wounds, the chances of its occurrence must of course be particularly favourable if the surface of a wound is quite fresh, as from the bite of poisonous animals or from incisions made experimentally for the introduction of drugs and poisons. The substances so applied then come to some extent into direct contact with the openings of the divided blood and lymph vessels; an *intra-vascular injection* of them occurs, in a certain measure, or a kind of medicinal infusion, a return to which in the hypo-

dermic method also has latterly been attempted. Absorption may, therefore, in such cases, corresponding with the number and size of the divided vessels, not only be very complete, but may follow with extraordinary rapidity; and, by reason of the sudden rush of a foreign substance into the vascular system, surprisingly severe general symptoms may under some circumstances show themselves, even when a relatively small dose of the medicine or poison has been administered. The case differs only in degree in the case of old wounds and ulcers when suppurating or granulating and cicatrising. The beginning of suppuration appears to lessen the rapidity of absorption, on which account certain surgeons (Dubois, Béclard, and others) preferred to use this particular time for the local application of various substances—arsenic paste, for instance; yet the difference, according to Bonnet's experiments, is not very considerable. At all events in every stage of the healing of wounds and ulcers absorption is possible, even when cicatrisation has occurred, if the cicatrix is recent, as is decidedly proved by observations on the effects of poisons when applied to recently healed blistered surfaces. On the other hand, however, experiments made by me showed a great uncertainty and want of uniformity of action in those cases in which medicines for therapeutic purposes were applied to already existing wounds and ulcers or fistulæ. This uncertainty was so strikingly prominent, particularly in comparison with the hypodermic method, which will hereafter be discussed, that, considering the facility with which the latter method may generally be made use of, the employment of existing wounds and ulcers as a concurrent mode of application is almost entirely excluded. Thus one grain of morphine spread on an ulcerated carcinoma of the mamma, or applied to a previously cleansed fistular sore in coxitis, proved in the experience of others as well as myself entirely ineffective, whilst, on the other hand, $\frac{1}{6}$ of a grain injected subcutaneously in the vicinity of the disease lessened the pain and gave the patient several hours of sleep. Although, as we have seen in the case of recent wounds, absorption proceeds easily and quickly—indeed, in some circumstances almost too quickly—yet scarcely anyone would dream nowadays of making incisions or other wounds of the skin artificially for the purpose

of the endermic application of remedies, in preference to the hypodermic method, in which the wound is so much smaller.

We shall now consider the various methods characterised as endermic in the narrower sense. Their importance as yet is only a historical one. They were called forth by the evident imperfection and difficulty of absorption in the epidermic methods, and might on their own part be regarded as more or less successful efforts at subcutaneous injection, and as precursors of the hypodermic application of remedies. An independent justification of their value in the therapeutics of to-day is no longer necessary in my opinion, and we may therefore pass them over with a short notice. The first and most commonly used of these methods was designated by its authors, Lembert and Lesieur (1823), the *méthode endermique*, or, more exactly, the 'emplastro-endermic method.' The procedure is as follows: the epidermis is, by means of a vesicant, to a greater or less extent removed, and the remedy is applied to the cutis in a solid or fluid form (as solution, powder, ointment, liniment, &c.) In this way undoubtedly there is procured a better absorptive surface, but accompanied by a dermatitis leading to suppuration, which consequently causes a great uncertainty and want of uniformity in the absorption. Moreover, when the usual vesicants are made use of, the method is somewhat tardy, and in cases in which a rapid curative or palliative action is of importance—for instance, in neuralgia and cramps—it is not very efficient. It is true that this blistered surface can be repeatedly utilised by keeping it open for a long time by means of irritating substances which promote suppuration, but then the evil of a very uncertain and unequal absorption makes itself all the more strongly felt, and the general effect of the drug can never be counted on beforehand. In order to bring about the denudation of the cutis more rapidly than is done by the usual epispastics, various modifications have been proposed, which, however, have been still less adopted in medical practice. To such proposals belongs Mayor's hammer—an iron hammer, or some other piece of metal, which is dipped in boiling water, and then pressed for a short time on the surface of the skin, when blisters are almost instantaneously formed. Another, somewhat slower, method

was practised by Trousseau and Pidoux in the endermic application of remedies, viz. the removal of the cuticle by means of ammonia, in the form of Gondret's pomade or strong ammonia. Pledgets of cotton-wool saturated with ammonia are applied to the skin and covered with a watch glass, after which the cuticle becomes puckered and may easily be rubbed off with a piece of linen. Caustic potash also was used by Gualla in the endermic application of curara in tetanus, &c. Finally, the proposal that has been repeatedly made, even very lately, of drawing through the skin small threads or silver wire covered with a solution of the drug may be mentioned, though this method is more nearly allied to those of inoculation and implantation.

The endermic method found, specially through Piorry, Valleix, Trousseau, and others, ready access into practice, and enjoyed, until the rise of subcutaneous injection about twenty years ago, a tolerably high reputation. As was afterwards the case with the hypodermic method, the application of narcotic and sedative remedies, such as morphine, atropine, or veratrine, in painful local affections, especially neuralgia, curara in tetanus and other severe forms of cramp, and strychnine in paralysis, was regarded as the chief advantage of the endermic method; in isolated cases also quinine and stimulating remedies, as camphor and musk, were applied in this way. With the increasing use of the hypodermic injection, the emplastro-endermic method of Lembert and Lesieur, as also its later modifications, were compelled to retire into the background, and gradually (rare cases excepted) were entirely expelled from medical practice. Its principal disadvantages, when compared with the hypodermic method, consist in the much greater amount of pain accompanying it, in the trouble attending its application, and the local limits to its use, as well as in the slowness and uncertainty of the therapeutic action. The spreading of morphine and other narcotic alkaloids in the form of powder on the denuded cutis, or the endermic application of the drug in the form of ointment, is, according to my experience, incomparably more painful than the hypodermic injection of the same substances in a suitable solution. The application of quinine, about which I possess no observations of my own, is charac-

terised by physicians who have tried it as an extremely painful operation. At all events, owing to this circumstance, this method is restricted to a comparatively small number of applicable substances. The vesicant forms, if it does not chance to be indicated by the course of the disease, an entirely superfluous and troublesome complication ; when it is kept open for a long time it is accompanied by all the pain of a suppurating wound, in comparison with which the pain of repeated small punctures in subcutaneous injections is of scarcely any moment. Moreover, this method cannot be applied to all parts of the body, and we must therefore dispense with the possibility of a local action often in the very cases in which this is most desirable, e.g. in facial neuralgia and spasms of the eyelids, to say nothing of the fact that in neuralgias, reflex cramps, &c., it is possible, by means of hypodermic injections, to come much more closely into contact with the affected nerves and to exercise a more direct action on them. Absorption, even in favourable circumstances, when the vesicant has been freshly applied, takes place in general much more slowly and feebly than after the hypodermic injection of a similar quantity of the drug. After endermic application of $\frac{1}{6}$ of a grain of morphine, for instance, Trousseau observed the first signs of a narcotic action in 12 minutes ; after subcutaneous injection this is often seen to appear in the first minute, almost immediately after the injection. To this must be added the far greater uncertainty and unreliability of the therapeutic result. By means of $\frac{1}{2}$ to 1 grain of morphine, applied endermically, I could obtain no hypnotic effect in cases in which, with $\frac{1}{6}$ to $\frac{1}{4}$ of a grain applied hypodermically or $\frac{1}{4}$ to $\frac{1}{2}$ of a grain given internally, I could always produce such an effect with perfect certainty. Conditions which had been treated for a long time without the slightest benefit by means of suitable remedies, endermically applied, sometimes disappeared very quickly after the hypodermic injection of the same drugs. A case communicated by Waldenburg[1] of complete aphonia from paralysis of the vocal cords furnishes a very instructive example of this. Three weeks' consecutive endermic application of strychnine, amounting on the whole to 1·8 grain, had in this case not the slightest effect,

[1] *Med. Centralzeitung*, 1864, No. 21.

while by 11 injections, amounting altogether to $\frac{1}{3}$ of a grain of strychnine, a perfect permanent cure was effected.

Medicinal Inoculation and Implantation.

The administration of remedies by inoculation, i.e. by making very fine puncture wounds in the skin, forms a variety of the endermic method, although it approximates somewhat to the hypodermic method, and it may even be regarded as really a form of the latter, since the drug is brought by the varying depth of the inoculation puncture into direct contact sometimes with the cutis and sometimes with the subcutaneous tissue. We might therefore distinguish between an *endermic* and a *hypodermic inoculation*; but this distinction can scarcely be carried out in a given case, and, besides, the practical importance of the proceeding is, for the present, so extremely small that it is scarcely worth the trouble to follow out its minor forms more closely.

The term 'inoculation,' as is well known, was originally used in connection with the transference of the virus of contagious diseases by means of an artificial scarification of the skin, and, even before Jenner's time, in connection with the prophylactic inoculation of the matter of small-pox, as well as that of the syphilitic virus (after the discoveries of J. Hunter). To the domain of inoculation in this sense belong also the universally known prophylactic and therapeutic methods of vaccination and of syphilisation, the latter of which was introduced into practice especially by Sperino and Boeck. Yet we may abstain from any discussion of these special methods here, so much the more as the virulent ingredients of the vaccine and syphilitic matter, &c., conveyed by inoculation, notwithstanding their possible preventive or curative action, can hardly be spoken of as remedies in the stricter sense. Neither shall we have to occupy ourselves here with those methods which have reference to the application of inoculation, not for the purpose of a general action produced by absorption, but of a purely local, stimulating, caustic, or destructive action, to which belongs, for instance, inoculation of vaccine virus in chronic affections of the skin, lepra vulgaris, mentagra, &c. (M. Langenbeck), the treatment of telangiectasy by inoculation with vaccine

matter, or croton oil (Ure, De Smet), or tartrated antimony (Dubreuil), or by the use of caustic points (Maisonneuve), &c.

The inventor of medicinal inoculation in the stricter sense was Lafargue, physician in St. Emilion, whose first experiments date from 1836. He and his successors afterwards modified the method in many ways, and partly in such a manner as to approximate it to the dry injection of Bruns (vide infra). Lafargue's original method is the following: A mass of the consistency of pomade is made from pulverised drugs with the addition of a little water; the instrument (the usual inoculation lancet) is dipped in it, and a number of punctures or scratches are made close together on the part indicated by the pain or by the course of the nerves, until the quantity of the drug intended for the application is completely inoculated.

Lafargue afterwards substituted for this method of inoculation a somewhat more complicated method, in which the drugs were first applied in the form of small solid cylinders, which, on account of their hardness and solidity, warrant the appellation of 'tampons' (*chevilles*). The whole proceeding was afterwards designated 'inoculation par enchevillement.' These tampons or plugs, however, must be very soluble, and of so small a calibre that they can be passed into a very fine puncture wound. By way of illustration it may be stated that for their preparation $\frac{1}{6}$ to $\frac{1}{3}$ of a drop of a thick solution of gum (gum Arabic and distilled water, equal parts) is mixed with $\frac{3}{4}$ of a grain of atropine and a like quantity of sugar; the mass, of the consistency of a pill, is rolled out to a narrow cylinder 5 inches long, and this is divided into small pieces, $\frac{1}{10}$ of an inch long, and dried. Thus we make 50 cylinders, each containing $\frac{1}{66}$ of a grain of atropine, so that the dosage is sufficiently exact.

To carry out 'inoculation par enchevillement,' Lafargue at first made use of a kind of scarificator, afterwards of small steel needles with a trocar, or better still with a lancet, point. These are, like an inoculation lancet, entered obliquely to the skin, and a puncture $\frac{1}{4}$ of an inch deep is made; the lancet is then withdrawn, and immediately, with the help of the finger, one of these medicinal cylinders is pushed into the wound. If, with a very contractile skin, the small puncture does not gape sufficiently, the opening must be dilated with a fine cannula,

the lower end of which has a kind of niche for the reception of the cylinder. Whilst the physician fixes the cannula with the right hand, he pushes the needle into the cannula with the thumb and forefinger of the left hand and thus presses the cylinder backwards into the dilated puncture.

Artificial, tedious, and clumsy as these proceedings may now appear to us, we must not overlook the fact that their inventor was undoubtedly guided by a very just notion. He was anxious to procure a substitute—much to be desired in many cases—for the usual internal application of remedies, and at the same time something more complete and reliable than the epidermic and emplastro-endermic methods. This object is so important that, if it could be attained in no other way, we should unhesitatingly make use of 'inoculation par enchevillement,' with all its trouble and minutiæ. Only it appears very remarkable to us that the much simpler and more obvious method of hypodermic injection, the ultimate solution of this problem, should not have been earlier thought of. With regard to the first results of Lafargue's method, its author made them known to the Academy of Paris, especially those relating to its use in painful affections, neuralgias, &c. The reporter of these, Martin Solon, expressed himself in favour of the method ; also Valleix, Cazenave, Malgaigne, Hayem, Rynd, and others applied it with success. Trousseau recommended the use of small narcotic pellets instead of the medicated cylinders, and obtained good results therefrom in obstinate cases of sciatica. Under this head too we may place the method of administering medicines by drawing through the skin fine threads or silver wires covered with a solution of morphine, &c. (Crombie). In 1847, in Germany, M. Langenbeck made numerous experiments with the inoculation of drugs, in which he varied the method in many ways, according to the consistence of the remedy applied. He pushed solid drugs in the form of powders, pills, or ointments, or in that of small cylinders or discs, into a puncture about $\frac{1}{2}$ an inch long, and directed obliquely inwards, made with a small lancet in a moderately broad fold of skin, or else he laid them in a small but tolerably deep incision formed by division of a narrow fold of the skin. The first method, as carried out by means of a blunt wooden or fish-bone instrument,

approximates to implantation or dry injection; the second corresponds more to Lafargue's 'inoculation par enchevillement' or Trousseau's modification of it. In order, however, to keep the seat of inoculation open for the purpose of repeating the application, Langenbeck added to the drug from time to time small quantities of an irritating substance, such as musk, camphor, cantharides, croton oil, or tartrated antimony. The small incision is changed by such treatment into an ulcerating surface, from which the drugs pass into the blood, certainly with all the irregularity and difficulty formerly mentioned, caused by the process of suppuration and cicatrisation. Langenbeck, however, considers this method as peculiarly convenient, because the patients themselves or their relatives can easily undertake the repetition of this 'surface inoculation' by laying the medicines on the open wounds and covering them with sticking-plaster; the enlarged space, besides, permits the administration of larger quantities of drugs in this way. He applied fluid medicines in a similar manner by laying pledgets of charpie or cotton wool, saturated with the medicinal fluid, on the wounds, and keeping them fixed there with sticking-plaster.

The method described by Bruns, and characterised by him as *dry injection* or *implantation*, is another way of carrying out the aims of Lafargue, Trousseau, and M. Langenbeck. In this, the drugs are likewise applied in thin cylinders or plugs, for the introduction of which, however, a special form of implantation needle is used. This is furnished with a lancet point, like the stilette of subcutaneous syringes, and contains above it an open channel, in which the medicinal plug is placed. By means of a movable wire or piston within the hollow part of the needle, the medicated plug can be pushed forward, after the entrance of the needle into the skin, and thus be pressed into the wound. Lafargue had evidently already contemplated something similar, since he provided the cannula employed for the enlargement of the wound with a small cavity for the reception of the medicated cylinder (vide supra); the introduction of the latter was, however, promoted not by instrumental, but by digital assistance. Implantation may be used also for the attainment of local medication, especially for cauterisation, in which the caustic is introduced into the puncture in the form

of somewhat thick cylindrical plugs, by means of the implantation needle or a similarly constructed trocar.

Apart from isolated forms of application of the last kind, Lafargue's inoculation and the similar methods of Trousseau, M. Langenbeck, &c., have scarcely any therapeutic value in the present day. The authors of these methods had of course a right to be of a different opinion as to their permanent value ; and thus we need not wonder if, at a time when hypodermic injection had already attained general application, Lafargue still insisted energetically on the superiority of 'inoculation par enchevillement,' and Langenbeck upheld the advantages of 'surface inoculation.' I shall afterwards refer to the uncalled for and entirely unfounded objections made at this time to hypodermic injection. The relative value of these methods in their historical connection with the epidermic and endermic methods on the one hand, and the hypodermic injection on the other, has already been fully acknowledged. A posthumous controversy with the advocates of these methods, now that they have long since vanished from the scene, would hardly appear justifiable either on moral or practical grounds.

SUBCUTANEOUS OR HYPODERMIC ADMINISTRATION OF MEDICINES.

(HYPODERMIC METHODS.)

We characterise as subcutaneous or hypodermic methods of administering medicines those methods *in which the medicine is introduced in a suitable form into the cellular tissue lying beneath the skin.* Apart from the local action on the tissues aimed at in many cases in the application of irritating, caustic substances, &c., we have here chiefly to do with drugs which are applied for the purpose of bringing about a general action by absorption. For this end, as is proved by a superficial observation of the structure of the parts, the subcutaneous cellular tissue is in a peculiarly high degree suited, when compared not only with other layers of the external integument, but also with the usual organs for the absorption of drugs, as the stomach, &c.

The framework of the subcutaneous cellular tissue consists, as is well known, of interlacing bundles of connective tissue, including between them large meshes, which are again split up by means of finer bundles into smaller secondary spaces. These meshes enclose in most parts of the skin lobules of fat, which are developed in very unequal quantity in different individuals, and consist of aggregations of oval or polyhedral fat cells, between which a delicate network of blood capillaries runs. In many parts of the skin—such as the eyelids, ear, penis, scrotum—these lobules of fat are entirely wanting; in other parts they are comparatively but feebly developed. In the subcutaneous cellular tissue which contains no fat, the secondary spaces are crossed by fine bundles, or separate fibrils, of connective tissue, which in chromic acid preparations leave between them lacunæ, mostly three-cornered and filled with serous fluid. The distance of the separate bundles and fibrils from one another is a very unequal one, corresponding to the different quantities of juice contained in the subcutaneous tissue. The number of blood and lymph vessels is everywhere tolerably large. The arteries ramify, particularly in the lobules of fat, to every one of which there passes an arterial and venous trunk, united together by a capillary network. Large trunks of lymph vessels, whose finer extremities lie in the external layer of the cutis, are observable in the subcutaneous cellular tissue in many places. These possess blood vessels of their own (*vasa vasorum lymphaticorum*), two fine blood vessels, as a rule, accompanying the lymph vessels, and forming with their numerous capillaries a thick network around them (Biesiadecki). Probably also the lymph vascular system begins here with lymph spaces, partly open, partly closed, but provided with pores (*stomata*). To the category of the latter may also be reckoned the connective tissue spaces surrounding the vessels (adventitious lymph spaces), as also the meshes of the fibrillary tissue, filled with fluid.

Whilst the net-like structure of the subcutaneous tissue permits of an easy reception and diffusion of drugs introduced in a fluid form, even when large quantities are injected, the rapid absorption of medicinal solutions distributed over a larger

surface is decidedly facilitated by the blood and lymph vessels of the subcutaneous cellular tissue. Whether the blood vessels or the lymph vessels alone or both together act a prominent part in the absorption is by no means finally decided, notwithstanding numerous experiments in earlier and later times; yet it must be distinctly understood that, according to the latest views, the lymph vessels especially, and the canals for the tissue fluids which are connected with them, may be looked upon as channels for absorption, as well from subcutaneous cellular tissue as from serous cavities and parenchyma. These views are chiefly founded on the results of experimental pathological investigations with infectious substances, the absorption of which appears really to take place by means of the lymph vessels, whilst, on the other hand, the healthy wall of the blood vessels is not penetrated by them. In these experiments the question evidently turns especially on the absorption of organised bodies, such as the contagium of certain diseases, bacteria, &c.; their results, therefore, without something further, are hardly applicable to the discussion of the question of the absorption of fluid solutions of drugs or of pure fluids in general. Yet it does not admit of a doubt that absorption even of the latter must be immensely facilitated and accelerated if the fluid penetrate directly into the open stomata of the canals of the tissue fluids and of the greater lymph vessels, or even into the mouths of the open blood vessels, especially the veins of the subcutaneous cellular tissue. The latter event may, as we shall see, take place in an unintentional injury to a large vascular trunk; and we have then, strictly speaking, no longer to do with a hypodermic, but with an intravascular application of the medicine with an *intravenous infusion* of it, which must be accompanied with the characteristic symptoms of rapid and powerful action. Even the direct entrance of the medicinal solution into integral portions of the lymphatic system, which might be called *lymphatic infusion* of it, is hardly to be considered as belonging to the hypodermic method in the stricter sense. At all events it is attainable only in exceptional cases, and by the use of special apparatus and methods of operation (vide infra); whilst, in hypodermic application in general, the diffusion of the medicinal solution which first

ensues, and then the succeeding gradual, though relatively rapid, absorption of it, form the main feature.

The utilisation of the subcutaneous cellular tissue for the express purpose of producing the absorption of drugs is undoubtedly of modern date, even though isolated observations, accidentally made on men and beasts, go back to a much earlier period. To these belongs the statement in *Pepys' Diary*, May 16, 1664, that Pierce and Clarke are said to have observed the appearance of narcosis in a dog after subcutaneous application of opium. My impression from the famous experiments of Fontana, with regard to snake poisoning,[1] was not that, in performing them, a definite and conscious application of the poison to the subcutaneous cellular tissue had been made. Fontana rather made small incisions first, and then pushed poisoned probes or arrows into the muscles of the animal; a method, which may be compared with the injections, lately proposed for therapeutic purposes, into the muscles (for instance, of morphine in traumatic tetanus, according to Demarquay). Even in the earlier investigations of Claude Bernard and his followers on arrow poisons and other toxic substances, in which the latter were applied by means of incisions, they do not appear to have thought, in practising this method, of drawing a sharp distinction between the superficial and deeper layers of absorption. On the other hand, Lembert, the inventor of the emplastro-endermic method, seems already, from a therapeutic point of view, to have thought of the possibility of an injection of medicinal substances into the subcutaneous cellular tissue. It has already been mentioned that the methods of inoculation and implantation practised by Lafargue, Trousseau, M. Langenbeck, and Von Bruns were partly intracutaneous or endermic, but also partly subcutaneous or hypodermic modes of application; these methods, which in reality possess only an historical interest, may therefore be viewed either as offshoots of the endermic method or precursors of the hypodermic method in its narrower sense. Already Lafargue had, at least, charac-

[1] *Beobachtungen und Versuche über die Natur der thierischen Körper.* German by Hebenstreit. Leipzig, 1785.

terised his *inoculation par enchevillement* expressly as a hypodermic method. Rynd, in 1845, and M. Langenbeck claim priority, however, for hypodermic injections. The latter, according to a paper, not published, it is true, until much later, injected narcotics through a puncture made by the very fine trocar of a small eye-syringe long before A. Wood; he is said, however, to have very soon again exchanged this for surface inoculation, as described and recommended by him.

However this may be, a mode of subcutaneous application suitable to therapeutics can only be considered as existing from the time when so convenient a method as that of *injection* (*subcutaneous* or *hypodermic*) was discovered and by degrees generally adopted.

The real inventor of hypodermic injection is undoubtedly Alexander Wood, of Edinburgh; his discovery only accidentally coincides with the fact that Pravaz, in 1853, had made known his method of injecting liq. ferri perchloridi into aneurisms, and had described a small silver syringe for injecting the coagulating solution.[1] Wood, in 1853, while using a syringe of Fergusson's, similar to that of Pravaz, for injecting liq. ferri perchloridi in a case of nævus, lighted on the idea of injecting by means of this instrument a narcotic fluid (opium preparation, as Battley's sedative solution, &c.) into the cellular tissue surrounding diseased nerves. He hoped, in this way—and this must be enforced as the starting-point of manifold later controversies on this subject—to combine with the general action produced by absorption also a specific local action on the affected nerves, and believed that this was confirmed by a series of fortunate results in prosopalgia, intercostal neuralgia, sciatica, &c. This method of treatment, however, on its first publication in the year 1855, seems at first to have been but little noticed in England, and not at all elsewhere. One of Wood's first imitators was B. Bell, who, besides preparations of opium, used also atropine in cases of neuralgia, and at the same time made the observation, so valuable to therapeutics, that the toxic symptoms caused by atropine disappear if morphine be subsequently injected. More extensive experiments

[1] *Comptes rendus de l'acad. des sciences*, Jan. 3, 1853.

were made by Ch. Hunter, one of the most energetic advocates and promoters of the new method, who, however, at the same time stood up as the opponent of its local action, and in doing so placed himself in opposition to Wood's original views. Besides the remedies already mentioned, he employed subcutaneously also tincture of aconite, tincture of cannabis indica, chloroform, &c. From numerous observations on men and animals, he inferred that the injected substances not only acted much more rapidly and energetically than when absorbed from the stomach, but acted under conditions in which a general action from their internal use could not be counted on. He pronounced hypodermic injections of narcotic and sedative remedies to be peculiarly suitable for the object intended, and on the other hand, in conformity with his opinion above mentioned, he regarded the locality of the injection in general as immaterial, and only recommended that it should be frequently changed, in order to guard against the secondary local consequences of the injection. Further, mostly casual, communications were made in the following years by Fuller, Cadwell, Rynd, Walker, Ogle, Crane, Spender, Duckworth, and several others.

Although Bertrand in 1857 had given in Germany a short account of Bell's experiments, it appears at first to have met with no attention—at least until 1860 we do not find that there was a single literary publication on this subject. On the other hand, in 1859, Béhier had managed to gain an introduction of the method into France. In his communication on the subject, addressed to the Academy of Paris, he reports the cases of 60 patients treated in this way. Of these, 53 were cases of neuralgia or painful affections of various kinds, and 7 were cases of paralysis. The former were treated with atropine, which in France enjoyed greater favour than morphine; in 31 of these cases he was completely successful. The paralysis was treated with strychnine. Béhier arrived at the same results as Ch. Hunter: hypodermic injections act much more quickly and surely than any other form of application, including the endermic method, and are therefore to be recommended not only in neuralgia and paralysis, but also wherever the object is to effect as quick and powerful a general action as possible.

Becquerel, Hérard, Courty, and others confirmed this favourable opinion, and furnished further proofs of the effect of narcotic injections in neuralgia and of strychnine in paralysis. The Italian War carried on at this time also gave an impetus to the hypodermic application of morphine, atropine, and curara in tetanus, from which, in certain cases, splendid results were obtained.

Very important also was the improvement of the apparatus used for hypodermic injection by the Parisian instrument makers, Charrière, Matthieu, and especially Luer; subsequently also by Leiter, who, by the introduction of inexpensive vulcanite, perhaps most of all contributed to render the method popular.

In America, the efforts of Ruppaner, in 1860, secured recognition of the value of hypodermic injections in the treatment of painful local affections, such as neuralgia, gout, &c. Langer also proposed the hypodermic application of quinine in intermittent fever, cholera infantum, typhus, &c., a mode of treatment which did not find an entrance into Europe till a later period. At the same time successful experiments with the new method were made in the hospital at Copenhagen. In Germany also it at last met with attention. In 1860, A. von Franque gave an account of forty-five cases of various affections, mostly neuralgic, which had been treated in this way. A more thorough work by Semeleder appeared in the following year, who, in numerous cases of disease, for the most part surgical, substituted the hypodermic injection of morphine for the internal use of it. He saw considerable benefit result from doing so, both in producing general narcosis and in relieving local pains in neuralgic, inflammatory, and other painful local affections, and even in producing local anæsthesia in minor operations, such as the application of caustic, &c. Further communications, particularly on the anti-neuralgic employment of opium, morphine, and atropine injections, &c., were made in the period that followed by Lebert and Türk, Scholz, Von Jarotzky and Zülzer, Stoffella (Oppolzer), Hermann, O. von Franque, and others, who individually furnished many a valuable contribution, without, however, adding anything essentially new; and the same thing is true of the gradually increasing flood of casual communications of the following years. As marking a new

epoch, on the other hand, is a larger publication of Von Graefe's in 1863, which is worthy of prominent notice, since the special indications of the method, as laid down after the observation of a great many cases, are for the first time clearly and thoroughly defined, though only in relation to ophthalmic practice, and only with respect to one remedy—morphine. In the same year, 1863, the Hufeland Society announced, as the subject of a prize thesis, 'The Action and Therapeutic Application of Hypodermic Injections based on Physiological Experiments and Clinical Experience.' The prize for the solution of this question was awarded to the author of the present work. The slow naturalisation and extension of the hypodermic method, which is evident from the historical sketch here given, and which was then complained of and accounted for by me,[1] supplies the best refutation of the charge lately brought against it—that indiscriminating enthusiasm for this new remedy has prepared the way for many later abuses of it.

A further history of the hypodermic method would be of little real benefit. It might have an endless number of names to record, but on the whole it would make known only an extensive, scarcely an intensive development. Even the former did not progress uniformly, but, as it were, intermittently, according as accidental causes, viz. epidemics, the appearance of new remedies suitable for subcutaneous injection, and such like, concentrated attention temporarily on one or another department of hypodermic therapeutics with more or less success. The past fifteen years afford examples in considerable numbers. Apart from the already mentioned anti-tetanic employment of curara, we have only to call to mind the hypodermic application of mercury, especially of the sublimate in syphilis, which, after isolated earlier experiments, was elevated to the rank of a prominent anti-syphilitic mode of treatment by the comprehensive investigations of Lewin; the extensive use of injections of morphine in cholera, occasioned by the epidemics of the years 1866 and 1867; the hypodermic administration of stimulating remedies, such as ether, musk, camphor, benzoin, &c., which was partly connected with these epidemics; the application of

[1] See the preface to the first edition of my *Hypodermatische Injection*, Berlin, 1865.

subcutaneous injections of strychnine in amblyopia and amaurosis, first practised in detail by Nagel in 1871; the subcutaneous injection of preparations of ergotine in cases of aneurism, internal hæmorrhages, diseases of the uterus, especially myoma; the therapeutic use made in the last ten years of hydrate of chloral, apomorphine, carbolic acid, and pilocarpine in the form of hypodermic injections, which mode of administration has proved in all cases the most suitable for certain of these remedies, and for others appeared to be really demanded by certain special indications.

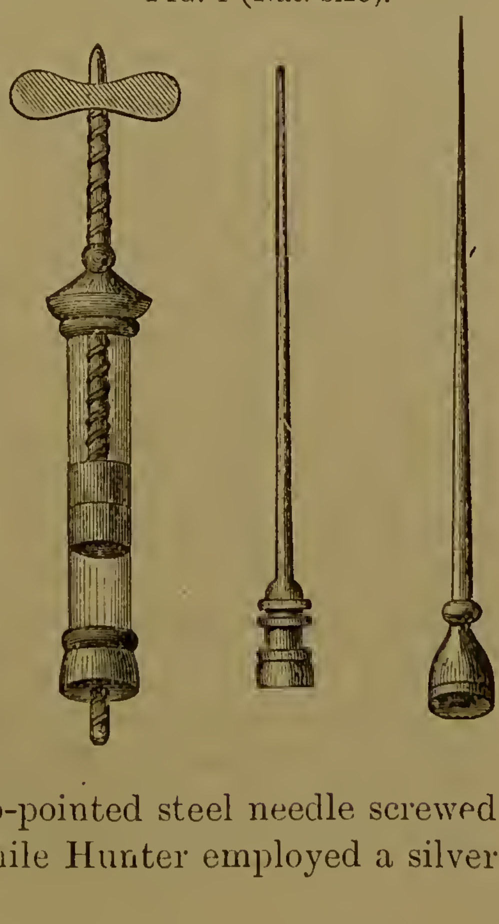
Finally, such a historical survey would at least have to point to various applications of the hypodermic injection, overstepping partially, it is true, the narrower and usual sphere of subcutaneous application of remedies, and yet in other respects there could be no hesitation in acknowledging the therapeutic value of these. To these belong especially the numerous experiments with the hypodermic injection of the most different remedies for the attainment of purely local action on the tissues, especially for obtaining local irritation in order to create an artificial inflammation which would act as a counter-irritant, such as Luton, from the year 1863, had proposed under the title of '*Substitution parenchymateuse*,' as also experiments for the purposes of local antisepsis and antiphlogosis. In many respects also we may consider as belonging to the domain of hypodermic therapeutics the injections of very various substances into tumours, especially those of a malignant nature (carcinoma, according to the proposals of Von Thiersch and Nussbaum), also into angiomata, strumous swellings, cysts, enlarged lymphatic glands, &c. However, a sharp boundary line must be drawn here, and we must definitely separate injections of this kind, *interstitial* or *parenchymatous injections* made into the tissue-spaces of new formations or the parenchyma of the lymphatic glands, from hypodermic injections and subcutaneous applications of remedies in general. The domain of the latter is, on the other hand, approached by the experiments which have lately been frequently made with subcutaneous injections of nutritious substances, fat, milk, &c., and even blood, though here again we have scarcely anything to do with an application of remedies in the stricter sense.

Instruments, and Manner of Procedure, in Hypodermic Injection.

For the purpose of hypodermic injection, instruments were used in the first period mostly of the same type as that employed by Pravaz for injecting liq. ferri perchloridi in cases of aneurism (syringes of Fergusson-Wood, Hunter, Travoy, Pravaz-Béhier, Charrière, and others). The injection syringes made after the Pravaz type agree in this, that the movement of the piston and the expulsion of the fluid is accomplished by a *screwing* motion, and in such a way as that, with every half turn of the piston, one drop of fluid passes out of the cylinder of the syringe. This was undoubtedly suitable for the injection of chloride of iron in aneurisms, in which the fluid must be measured off by drops; but for ordinary injections it soon proved to be a useless hindrance and obstacle, on which account this mechanism was gradually given up, and was replaced by a simple sliding movement of the piston.

The best known and most widely used of the older instruments is the syringe of Pravaz, as modified by Béhier (fig. 1), with which I myself at first performed numerous injections. The capacity of such a syringe, which I tested, amounted to 0·596 grm. (9·19 grains) of distilled water at 13°C. The contents were emptied by 30 half, or 15 complete, turns of the screw, so that at every turn 0·0199 grm. (0·306 grain) came out, and therefore much less than we are accustomed to regard as the average weight of a 'drop' of an aqueous fluid. The barrel of the syringe was of glass and the other mountings were of silver. For puncturing the skin,

Fig. 1 (Nat. size).



Wood made use of a hollow, sharp-pointed steel needle screwed on to the point of the syringe, while Hunter employed a silver

needle with an inflexible golden point; but the instrument used for this purpose by Pravaz was a fine cannula and trocar, the former being attached by screwing it to the point of the syringe after the removal of the stilette. The mounting of the cannula was of silver, and it was furnished with a mother screw for the reception of the point of the syringe. Usually two cannulæ, fitting one into the other, were supplied with the apparatus. The injection with this instrument is made in the following manner. The barrel of the syringe is, so far as necessary, filled with the fluid to be injected, whilst the fluid is either sucked up from beneath by screwing back the piston, or the upper end of the syringe is screwed off, and the piston is removed, and the fluid is poured in from above. The skin over the part to be injected is then raised by the left hand, so as to form as large a fold as possible, and the trocar is pushed so deeply through the whole thickness of it that the point can be moved freely about in the subcutaneous tissue; the fold in the skin is then allowed to sink, and the stilette is drawn with a sharp pull out of the puncture. Whilst the cannula is being held by the thumb and forefinger of the left hand, the glass syringe, previously filled, is carefully attached to the cannula by screwing, so that neither air can enter nor fluid escape. The contents of the cylinder are now expelled by turning the piston from left to right. After this has been done, the left thumb is placed on the puncture beside the cannula, and the latter is removed along with the syringe by a quick movement of the right hand, after which the left thumb immediately compresses the opening of the puncture and pushes the skin over it, in order to prevent bleeding or the escape of the fluid. (The addition of a second finer cannula, fitting into the first, and which could be introduced into the other after removal of the stilette, was intended to prevent, or as far as possible lessen, the entrance of air into the puncture—a somewhat superfluous and needlessly complicating arrangement for ordinary injections.) The whole mechanism of these older syringes with a screw-working piston and a trocar should for several reasons be rejected for ordinary subcutaneous injections, and they are now pretty generally replaced by an instrument with a direct piston movement and a lancet needle, which we

shall presently describe. The chief disadvantages are the following. The injection, on account of the screwing on of the syringe and the turning of the piston, which has to be so minutely carried out, takes a considerable time for its perform ance; this is of some importance, not only on account of the loss of time, which is of little consequence, but because injections are thus made much more troublesome and painful for sensitive patients, and are often, especially in children, insane persons, and others, rendered difficult or even impossible by the restless movements of the patients. Besides, in such circumstances, an entrance of air or a partial escape of fluid might easily happen during the necessary manipulation in screwing the syringe on the cannula; the puncture made by the trocar is also larger, more painful, and more likely to be accompanied with disagreeable local effects. I must decidedly deny that the slow entrance of the fluid, as has been represented by many, is an advantage of the method; the completion of the operation as quickly as possible is every way preferable, on account of its sparing pain and of the greater safety of the procedure. A uniform distribution of the fluid in the subcutaneous cellular tissue, without stretching and tearing of the latter, can be quite as fully attained when the time of the injection is shortened.

The three great Parisian instrument makers vied with each other in inventing improvements of the syringe of Pravaz-Béhier. Charrière substituted for the trocar a needle which could be screwed like Fergusson-Wood's. Matthieu fitted to the end of the barrel of the syringe, which has a central hole for the passage of the handle of the piston, a so called bayonet lock which could be lifted at pleasure. By raising it up, the screw movement of the piston could be changed into a simple direct movement, whilst by its closure the screw mechanism could be immediately restored. The screw movement served for filling the syringe by sucking up the fluid; the direct movement of the piston, on the other hand, served for its expulsion. Matthieu made, moreover, the movements of the screw more uniform. His syringe contained 4 c.cm. (1 drachm) of fluid, and the piston rod had a scale numbered from 1 to 4; thus each division corresponded to 1 c.cm., and, as the number of

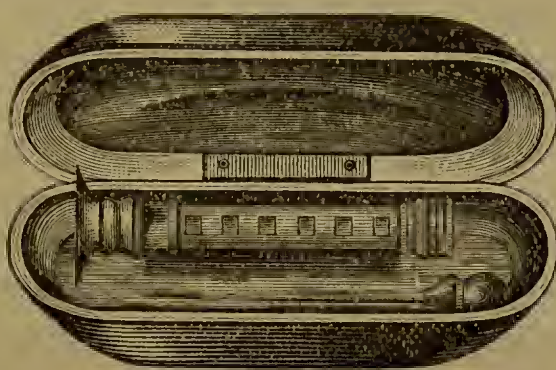
turns of the screw amounted to 40, each turn displaced $\frac{1}{10}$ of a c.cm. In this way a more exact dosage of the injections was made possible (*seringue décimale hypodermique*).

Luer went still further, for he set the screw entirely aside and replaced it by a direct moving piston. 'Luer's syringe,' which attained such great popularity and was justly valued on account of its precision, underwent, it is true, in the course of time several other modifications; in the description of it I adhere to the older models, dating from the year 1864 (fig. 2). The barrel of the syringe is of glass mounted with silver; the piston rod is furnished with a well-fitting leather valve, and bears a graduated scale, which is numbered, in multiples of 5, up to 45. The capacity of such an older syringe I found to be, at 13° C., 0·88 grms. (13·58 grains); the division would accordingly give for each degree of the scale 0·0195 grm., which, however, requires a small correction, inasmuch as a portion of the cylinder, corresponding to about 5 divisions of the scale, is covered by the leather valve of the piston rod even when entirely drawn back, and therefore remains empty of fluid. In the earlier instruments of Luer the piston rod bore a mother screw which could be screwed to each point of the scale, and which was to serve for fixing the piston; afterwards, however, this was justly left out as superfluous. The puncture is made by means of a hollow needle, attachable without screwing to the point of the syringe, and which is furnished with a slightly bent or straight lancet point. This is about two inches long, of steel or gold, and is mounted with silver. Luer's earlier cases usually contained a steel and a gold needle; the latter, however, proved unsuitable from its great flexibility. A bundle of fine silver wires was added for the purpose of cleaning the needle. The price of such a case formerly amounted to 21 to 24 shillings. German instrument makers now construct such a syringe for 9 or 10 shillings.

FIG. 2 (Nat. size).

As to the changes in Luer's syringes made in the course of time, and also adopted by Luer himself, I consider only two as important improvements. One is the use of vulcanite, introduced by Leiter, of Vienna, as a substitute for most of the metal hitherto used, and thus suitable for the construction of the graduated piston rod and for the ends of the syringe, as also for the mounting of the cannular needle (Tiemann even constructed syringes with vulcanite barrels instead of glass ones). By this means the syringes, with nearly equal durability, were considerably cheaper. The present price of a vulcanite syringe in a vulcanite case (fig. 3), with a steel or gold-pointed needle, amounts to four or five shillings. Unfortunately the increasing cheapness has resulted in a deterioration and careless construction of the instrument; a complaint which must be made especially of a large number of German instrument makers. 'Cheap and bad' is in this trade often still an unquestionable truth.

Fig. 3.



In many instruments, only the mountings of the syringe and of the cannula, and not the piston rod, are made of vulcanite. While in the older syringes the vulcanite mountings were connected with the cylinder by means of a cemented screw, they are now, on the other hand, fitted by grinding, whereby a more certain joining is made (e.g. the syringes made by Goldschmidt, of Berlin).

Still more important to me appears the second change, which unfortunately has not been generally adopted, and which consists in this: *the cylinder is made to hold exactly* 1 *c.cm., or pretty nearly* 1 *grm., of distilled water at the ordinary temperature, and is divided into decigrammes either on the piston rod or outside on the glass of the barrel.* It is a simple demand of sound reason that the hypodermic syringe which is so much used should coincide in this respect with the universally received standard weight and the corresponding titrated medicinal solutions; a demand which, as a rule, has

been attended to in the later syringes of Lucr and Leiter, although, on the other hand, our native instrument makers appear to take up this idea for the most part with great hesitation and reluctance. *Every physician who wishes to compel the instrument makers to the adoption of this graduation, besides sparing himself doubt and needless difficulties in calculation, ought always to purchase instruments divided into decigrammes (minims, if English), and capable of holding* 1 *c.cm.* (15 *mins.*) *of fluid.* But he must not forget to test it for himself, and he ought never to trust to the statements made to him. Lately, I was witness to the fact of a syringe being bought and sold as one containing 1 c.cm., which, on being examined, was found to contain 1·80 c.cm. of distilled water at 68° F.

For special purposes, as for injection of corrosive sublimate in syphilis, a syringe of greater capacity (Lewin) may be desirable under certain circumstances. For similar reasons Anel's syringe, intended for injections into the lachrymal sac, has been used. For injections of greater quantities of fluid, Hueter's infuser is the most serviceable (vide infra).

Of little essential importance, but yet worthy of notice, are the attempts lately made to manufacture the little hypodermic syringe so that it can be carried in the waistcoat pocket; or, on the other hand, by the addition of portable medicine bottles, to more or less add to the number of the medicines that may be carried by the practitioner for hypodermic use. The first object is attained in an instrument constructed by Leiter. This syringe is protected in a brass case; it occupies little space, and is so arranged that after use the detached cannula can be pushed into a central hole in the piston rod at the top of the handle, so that its point fits into a plate placed at the lower end of the piston rod. In order to make it possible to carry about fluid medicines in one's pocket, cases have been made of such a form as to contain one, two, or even four vials of the most commonly used solutions. Leiter, and also Goldschmidt, make vulcanite cases of a flat shape, with one or two vials, which are very suitable for the purpose; the point of the syringe can be dipped into the bottle, and the syringe may be filled by drawing up the piston in a vertical position. Tiemann, of New York, has lately recommended air-tight flasks, which

need not be opened at all for the purpose of filling the syringe; the latter is fitted into an opening in the side of the stopper, when the bottle is overturned, so that the fluid can be drawn into the barrel of the syringe. In order to fill the bottle again, the stopper can be taken out by giving it half a turn.

Instead of needles of steel, silver, or gold, needles of platinum-iridum have been proposed. These, it is true, are considerably dearer, but by heating them they can be easily cleansed. It may be remarked, by the way, that they are only to be got in Paris. Latterly Leiter has used cannulæ of platinum plated with steel and afterwards with nickel to prevent oxidation. To unite the needle immovably with the syringe, as Coxeter, for example, and, in conjunction, it is true, with another kind of construction, Bourguignon and Rynd wished to do, is, in general, of no advantage. The efforts made by Bourguignon, Rynd, and a few others to substitute a new arrangement for the piston of the syringe, which certainly becomes easily useless and troublesome by deficient confinement of the fluid, have not led to any practical results, if we leave out of sight the infuser, to be afterwards considered. Rynd wished to use the pressure of the fluid itself in driving out the contents of the syringe so soon as the escape is permitted by the springing back of a needle immovably connected with the syringe. Bourguignon fastened at the upper end of the glass cylinder an arrangement, like the finger of a glove, which could be raised or depressed at pleasure—raised to fill the syringe and depressed to empty it. In a similar way, Von Graefe and Beigel wished to suck in the fluid by an indiarubber bag, and then again cause it to escape by compressing it. But these arrangements are not more durable than the usual syringes; moreover, they render a precise dosage difficult, and are apt to permit the introduction of quantities of air into the subcutaneous tissue along with the fluid. Leiter has lately proposed a construction reminding one of Rynd's syringes, but more complicated than they are, by which it is asserted that the pain of the puncture is avoided and the entrance of the cannula for the requisite distance and direction under the skin is exactly regulated. For this object, there is in an outer tube a spiral spring which, by being pulled back by a catch, can be

coiled tightly up and then let go by a light pressure on the catch. The syringe is filled and pushed into the tube along with the screwed-in cannula, the spring being coiled up; then a second tube, which is graduated and provided with a funnel-shaped end, is screwed on to the first. When the spring is let go, the syringe is discharged, and the cannula driven out of the funnel up to the mark decided on. The pressure of the spring then immediately acts upon the piston of the syringe and presses out the fluid quickly and evenly. A somewhat too rapid pressing out of the fluid may be moderated by holding back the catch of the spring. The whole proceeding is said to require about 2 to 3 minutes.

Injection with Luer's or the ordinary Leiter's syringe is made in the following way. The syringe is filled up to the extent decided on, by drawing back the piston and sucking in the fluid, poured into a watch glass or some such article; it is best done before attaching the needle. The needle is then attached, and the air still contained in the instrument is driven out by turning it with the point directed upwards, and gently pushing the piston until a drop of fluid escapes from the opening at the point of the needle. The latter is then pushed sufficiently deeply into the skin by raising a fold of it, and the contents of the syringe are emptied by pushing down the piston; the instrument is then quickly withdrawn and the puncture closed with the thumb in the way formerly described.

The distribution of the fluid in the subcutaneous tissue may be assisted by gentle pressure with the finger in case of necessity, especially in parts where the thin and movable skin easily yields to the pressure of the injected fluid, and swells up in a bladder-like manner, as may be the case, for instance, with the temporal region. If several syringefuls are to be injected, Walker would allow the instrument to remain in the tissue; and he would only unscrew the piston, and fill the syringe again from above. I consider it, however, much more convenient and suitable, in case one has neither a larger instrument nor an infuser at command, to draw the needle entirely out and choose a fresh place to puncture. To close the opening with sticking plaster, collodion, &c., is, as a rule, quite unnecessary; it is of use at most only in unprotected

portions of the body, such as the face, as also in possible capillary hæmorrhages of vascular portions of the skin.

Special care ought to be taken to keep the instrument clean and in good order. Every one who requires to perform frequent injections knows how annoying it is to have an instrument in bad condition, and which is found to be useless when wanted. Indeed, we may assert that the task which in this method is the most difficult, and costs most time to the physician, consists in keeping himself in possession of an instrument at all times serviceable and efficient. The syringe must, after every employment of it, be repeatedly washed out with pure water and with air, and carefully dried, and the piston often taken out and soaked in hot water; to grease it, as many recommend, appears to me unnecessary, and not at all advisable, lest it should dirty the inside of the glass cylinder. Still greater care should be spent on the cleansing of the cannula, especially if acid solutions, metallic salts, &c., have been used. The cannula should be repeatedly washed out by a fine but powerful stream of water; the moisture still adhering to its walls should be removed by a strong current of air, and a suitably fine, stiff wire of gold or silver should be introduced and allowed to remain till the next injection, in order to guard against the gradual narrowing of the lumen by oxidation. The metallic wires usually sold for this purpose are much too flexible, and as a rule can each be used only once. To cleanse the cannula I employ with advantage a fine kind of file, such as is generally used by watch and instrument makers. This must be many-cornered, rough, made of not too hard steel, about two inches long, or rather more, and should be fitted with a sufficiently strong wooden handle.

Hypodermic Infusion.

In the foregoing pages several forms of apparatus have been mentioned, in which the object was to replace the action of the piston by the pressure of the fluid itself, and to secure the entrance of the latter into the subcutaneous cellular tissue, by letting go a spring (Rynd), by depressing a finger-shaped piece of indiarubber (Bourguignon), or by compressing

an indiarubber bag (Von Graefe, Beigel). These efforts, assisted at the same time by a suitable alteration of the hollow needle, appear to be simplified and perfected in the instrument (*infusor*) recommended by Hueter for the purpose of 'parenchymatous injection and infusion' of larger quantities of fluid, especially solutions of carbolic acid. The principal part of this instrument is formed by a graduated open glass tube of 1 cm. ($\frac{1}{5}$ inch) diameter, divided into c.cms. and half c.cms., and which up to the division marked 0 contains about $\frac{1}{2}$ ounce of fluid, and at its lower end is drawn out into a point. Over the latter is drawn an indiarubber tube, of the calibre of a thick drainage tube, 65 cm. (25 inches) long, whose other end is attached to a hollow needle, which is made with numerous openings (about 50) in its lower part. It is thought that the numerous openings cause an easier penetration of the fluid into the finest lymph vessels, and thus a direct lymphatic infusion is produced, inasmuch as the probability is that at least some of these openings will be found opposite larger tissue spaces or the mouths of the lymph vessels. In using this instrument, which I have found to be very suitable in experiments on animals, the indiarubber tube with the needle is first attached to the glass tube; then the upper end of the needle is grasped with the fingers of the right hand, and at the same time the tube is tightly compressed close above the needle after the manner of a pincette; the left hand holds the glass tube filled with fluid and somewhat raised. (The application of a stopcock to the connecting indiarubber tube might, in many cases, contribute to the convenience and safety of the operation.) After the needle has been sunk into the tissue, the height of the fluid is observed with the eye, and the compression of the tube is now removed. The height of the fluid now suddenly falls about $\frac{1}{2}$ c.cm. by dint of the filling up of the small indiarubber tube, which has hitherto been closed by compression with the fingers. Then follows a tolerably slow and regular sinking of the fluid, while by its own pressure it is flowing slowly into the tissues. If the flow at times stops, then a rotatory motion may be given to the needle, in order that its openings may come to be opposite other parts of the tissue. The quantity of fluid injected may at any moment be easily

ascertained by a look at the glass tube; in doing so, the small quantity necessary to fill the front part of the indiarubber tube—about $\frac{1}{2}$ c.cm. (8 mins.)—requires to be deducted from the whole quantity infused, as represented by the height to which the level of the fluid has fallen. If, for instance, the level of the fluid has fallen from 0 to 2 c.cm., then $2-0{\cdot}5=1{\cdot}5$ c.cm., which have flowed into the tissues. The infusor has one advantage over the usual injection syringes, viz. that of being able to introduce into the subcutaneous cellular tissue greater quantities of fluid, and therefore less concentrated solutions of drugs, which, in certain conditions, may be of undeniable benefit. Whether, as Hueter believes, it is also equal to the task, which physicians have attempted to accomplish by direct introduction of aqueous solutions of medicines into the circulation (intravenous infusion), is another question, which does not occupy us here at present. At all events, 'lymphatic infusion,' as above practised, possesses the advantage of being very simple and convenient in its management, and allows of repetition at pleasure, as also of a more safe and gradual passage of the drug into the blood.

Local and General Effects accompanying the Use of the Hypodermic Injection.

We shall of course not take into consideration the local and general effects which are produced by the peculiar properties of the injected medicines, as, for example, the sedative action of narcotic injections. We have presently to do only with more or less noteworthy effects and accidents, to which the act of hypodermic injection, as such, directly gives rise, or by which, in exceptional cases, it may be accompanied.

Among the most common of such local effects, which are both unintentional and unwelcome, is the *pain* which may be caused by injury to the cutaneous nerves in making the puncture, and in the stretching and tearing of the skin and subcutaneous tissue in injecting the fluid, and also by the irritating character of the drug injected. If we leave out of sight the last factor (which we should endeavour in general to exclude as much as possible, by suitable choice, solution, and dilution

of the medicines applied), the pain otherwise suffered from the performance of subcutaneous injection is rarely very considerable. It is true it cannot be entirely avoided, but it may be considerably reduced by making the puncture as tenderly as possible, using for the purpose sharp-pointed, slender, and inflexible needles, and as far as possible preferring portions of the skin which, on account of rich development of subcutaneous tissue, facilitate the regular distribution of the injected fluid. Equally important for this object is the use of a pure, clear, and as far as possible neutral solution, containing no impurities or deposit of crystals, &c. Much might be said on this subject, which may appear trifling, but one must be a witness of the indifferent way in which, and the imperfect instruments and solutions with which, injections are often made by physicians, and latterly even by the laity, in order to hear without surprise the complaints made here and there of the great pain suffered from the injection of some common remedy which we ourselves have hitherto always found to be comparatively painless. It is, however, quite intelligible that we should not shrink from the use of strongly irritating, in themselves pain-exciting, remedies and solutions, if other indications demand this form of application; although recently in this respect, I think, the boundary line has often not been drawn sharply enough, and the *jucunde* of the well-known medical saying along with the *cito et tute* has not always been enforced as it ought. For instance, let the somewhat aimless use, in my opinion, of the subcutaneous injection of chloroform, hydrate of chloral, &c., be called to mind. On the other hand, with regard to the supposed painfulness of the injection, the circumstance must not be overlooked that the injection is very frequently employed in the case of patients who, in virtue of the nature of their disease, whether it be that it is in itself very painful, or that it is accompanied by lessening of the sensibility, or impairment or actual loss of consciousness, &c., are relatively little affected by the pain of the operation.

As disagreeable effects, of rare occurrence, must be mentioned regurgitation of the injected fluid from the opening o' the puncture, and hæmorrhage and injury to the larger blood and lymph vessels. Such effects may as a rule be prevented

by a careful performance of the operation with the precautions already described. *The escape of the fluid from the opening of the puncture* may, in certain cases, depend on this, that the opening of the needle is kept closed by the pressure of the finger, or that the direction of the puncture is unfavourable, as when it is from below upwards; but more frequently the cause is that the cannula has not been introduced far enough into the subcutaneous tissue, so as to move freely in it, or that, owing to the piston moving with difficulty, and the suspension of solid particles in the fluid, the expulsion of the fluid from the syringe takes place violently and suddenly, and some of it is then again forced out of the puncture by the side of the cannula. A capillary hæmorrhage from the puncture is pretty surely avoided, under ordinary conditions, by proceeding cautiously and avoiding dilatation in the withdrawal of the cannula, and by displacing the skin, and immediate compression with the thumb. On the other hand, in pathological conditions the distended venous capillaries of the skin may give rise to a very considerable hæmorrhage, as I have not unfrequently observed in cases of sciatica in the lower extremities of fat, plethoric individuals, suffering from abdominal disturbances and venous stasis. It is true this hæmorrhage is not of itself dangerous, and might even in questionable cases be regarded as a convenient depletion; yet still it is troublesome and casts doubt on the success of the injection, inasmuch as a portion of the injected fluid is easily washed out along with it. A careful choice of the seat of injection will, as a rule, prevent this undesirable occurrence; still one may certainly be at a loss if, on the one hand, the choice of the locality is materially restricted by the existing local disease and the special indications connected with it, and if, on the other hand, a more frequent repetition of the injection is required by the chronicity of the disease.

An accident, at all events, of still more rare occurrence, and of which, for my own part, notwithstanding my having performed injections innumerable times during seventeen years, I have never yet seen a good example, is the *penetration of the cannula into the lumen of a larger subcutaneous vessel (vein) and the change of the hypodermic into an intravenous injection.* Nussbaum, in 1865, first drew attention to the

possibility of this, and depicted in glowing colours the frightful consequences of such an involuntary medicinal infusion, partly from experiences he had himself undergone. Effects similar to those which Nussbaum had the opportunity of observing three times on himself, and as often on patients, are also mentioned by Schirmeyer, Feith, Chouppe, and recently by Schüle, who, rather curiously, attributes them to 'reflex action transmitted from the seat of puncture to the medulla oblongata.' All these observations refer exclusively to injections of morphine; and the puncture of a vessel and direct penetration of the cannula into a vein is, in this case, necessarily inferred from the immediate and exceedingly violent appearance of symptoms of morphine poisoning—formication, first in the hands, then in the whole body, redness of the face, sometimes also of the whole body, strong pulsation in the arteries, feeling of heaviness, sickness, and vomiting, swooning, sudden falling down, &c. However, when we look more closely at the cases under consideration, we find that sometimes maximal and even ultramaximal doses of morphine were injected (Chouppe, 0·03 grm., or $\frac{1}{2}$ grain; Nussbaum as much as 0·12 grm., or 1·8 grain). Schüle also remarks that the severer symptoms of shock appear so much the more frequently according as the injected dose is larger. Moreover, there is much else that speaks against the occurrence of injury to the vein; for instance, the statement made by Nussbaum, that he succeeded in *extracting a portion of the injected fluid* along with the blood *by drawing back the piston of the syringe.* I, at least, cannot rightly explain this to myself in the case of infusion into a vein, even were the power of the blood current in that vein ever so small, and considering also the pause, of certainly more than a few seconds, between the observation of the toxic effects and the extraction; I believe rather that the fluid in such cases had partly infiltrated into the alveoli of the subcutaneous tissue. At all events, we can imagine that in many cases the opening of the cannula may accidentally come to be opposite the mouth of a large tissue-canal, or one of the smaller stomata of a lymph vessel, and by that means a partially direct passage into the lymphatic system may take place (vide supra). Nor is this circumstance to be overlooked with regard

to certain of the above cases, that, in sensitive persons, even the puncture itself, or the injection of an entirely indifferent fluid, such as water, may produce sudden symptoms of fainting, as appears from communications by Krishaber, Peter, Semeleder, and others. Still more may the irritating character of the fluid employed for injection bring about swooning or shock-like phenomena in a reflex manner. To me the statement of Schüle with reference to this subject is interesting,[1] that he never again observed the severer form of 'respiratory and circulatory paralysis' after injections of morphine from the time that he ceased to use acidified solutions of morphine (acetate of morphine with addition of acetic acid).

To guard against the undesirable occurrence under consideration, Nussbaum recommends very slow injection and immediate drawing backward of the piston on the appearance of mischief; Chouppe, on the contrary, advises that we should first introduce the cannula alone and make sure that no blood flows out of it, and, if this occur, that we ought then to seek another place, or make a deeper puncture before beginning the injection. I, for my part, cannot attach to these proposals any great practical importance.

Münchmeyer believes that he has observed the *puncture of a larger lymph vessel.* He saw, after subcutaneous injection of distilled water, the rapid appearance of large, irregular, intensely itchy wheals or eruptions round the seat of injection, and tried to find the explanation of these in the distension of the finest lymph tracks, in consequence of an injection into a lymph vessel. I have seen the development of a good deal of erythema urticatum around the puncture follow each injection made on the anæsthetic side in a case of hysterical hemianæsthesia, but never, on the contrary, on the healthy side, and I leave it undecided whether there was perhaps here some question of a subparalytic condition of the finer blood and lymph vessels. Perhaps the circumscribed changes of the skin, which often occur in the immediate neighbourhood of the puncture, are to be explained in this way. Usually there appears after the injection, sometimes not until several hours after, a small red areola around the puncture, more rarely a small whitish swel-

[1] *Handbuch der Geisteskrankheiten*, p. 670.

ling, such as is left after the bite of a gnat or the sting of a nettle. These effects often continue from one to three days, while the puncture itself closes completely after a few hours and is at most perceptible only as a fine point. Exceptionally with a very tender sensitive skin, especially as over the face, the injection, without any specific irritating quality of the drug used, may result in the formation of a small nodular, mostly painless induration, in the neighbourhood of the puncture. All these effects, which are of little importance practically, are perhaps to be attributed to more or less limited distension of the canals of the tissues and finer lymph tracts opening into the puncture. They form, however, a gradual transition to those disagreeable effects of the injection, which we are accustomed to class as *local inflammatory* effects, and which lead to more or less serious destruction of the tissues, with ecchymosis, mortification, ulceration, or the formation of abscesses.

The fear that subcutaneous injection may result in local inflammatory effects is already somewhat old. Though Wood himself and his immediate successors do not seem to have felt it, yet Hunter in particular expressed the fear that, by *frequent repetition of injections in one and the same region of the skin*, inflammation and abscesses might easily be produced. This fear, I was able to say in my first discussion of the subject in 1865, is entirely groundless, because of the fact that I myself, in a case of mastodynia, during a period of two years and a half, had performed 1,200 injections of morphine in the neighbourhood of the breast affected with neuralgia, without ever perceiving any symptoms of local inflammation. All later observations have only confirmed my belief that the mere repetition of subcutaneous injections within a comparatively small area, need not in itself lead to bad local consequences. Where such appear they must, according to my firm conviction, be almost exclusively attributed to *the irritating character of the injected medicine or of the solvent employed.* That in this respect a good deal of error exists is proved by a glance into the daily practice of hypodermic therapeutics; and also the literature of the subject, so far as I have become acquainted with it, contains nowhere refutations, but rather numerous direct confirmations of my opinion. Nowhere will it

be found that the injection of pure water, or even of a clear filtered solution of morphine (made with water or glycerine), and not acidified, has resulted in phlegmon and abscess. That, however, on the other hand, from the injection of solutions of morphine in creosote (Rynd), or muddy solutions of extracts, such as extract of belladonna (Garrison), or solutions of quinine —which, as a rule, are very imperfectly prepared and easily become mouldy, as is reported by Gualla, Fischer, Steinhaus, Von Fillenbaum, Mitchell, and others—more or less abundant suppuration and ulceration ensue, can cause as little surprise as the appearance of similar accidents after the injection of violently irritating substances. As examples of the latter, which have in many cases produced local irritant effects and suppuration, may be mentioned veratrine, saponine, chloroform, hydrate of chloral, oil of turpentine, tincture of cantharides, nitrate of silver, tartrated antimony, concentrated solutions of chloride of sodium, iodide of potassium, &c.

In connection with the bad effects of locally irritating drugs and solutions, may be mentioned various statements on the appearance of tetanus after subcutaneous injection of quinine in intermittent fever (Fonssagrives, Devaine, Mitchell). These statements proceed exclusively from tropical regions (French colonies in the East Indies ; New Orleans), and possess, moreover, a character little to be trusted. Especially in the communications of the French physicians (Fonssagrives, Devaine), there seems, according to Sourrouille, to be every appearance of a confusion of diagnosis, seeing that cases of endemic tetanus, which is always present in Eastern Asia, especially in the marshy districts, were confounded with those of pernicious intermittent fever, and injections were even made in already existent tetanic fever. In the case reported by Mitchell from New Orleans it is stated that not until two months after the injection was a deep ulcer formed at its seat, and death followed with tetanic symptoms. Mitchell ascribed this to the locally irritating action of the watery non-acidified solution of quinine, and assures us that he has heard of several similar cases. It is, however, conceivable that a deposit of crystals of quinine, in imperfectly prepared solutions of that drug, might cause intense local irritation of the sensitive nerves, and might thereby reflexly excite tetanus.

Finally, the possibility of the conveyance of *infectious diseases*, such as syphilis, pyæmia, &c., by the use of syringes employed for hypodermic injection may be suggested—a possibility for which, it is true, no direct, well-grounded reason exists in the literature of the subject, but which, nevertheless, cannot by any means be denied. The means of guarding against this dangerous occurrence are self-evident. In hospitals and dispensaries great attention must always be paid to the use of hypodermic syringes; the cleansing of them ought to be carefully superintended, and the performance of the injections not entrusted entirely to the *Diis minorum gentium*, the subordinate physicians, or the attendants on the patients.

In connection with this discussion of the local effects of the injection, a few remarks, arising directly in part from it, on the *selection of the seat of injection* may find a place here. This indeed in a large number of cases is indicated by the locality of the affection, at least for those who, along with the general effect of the drug, caused by absorption, believe also in the local, especially the sedative, effect of the injected drug—a question the answer to which will occupy us further on. In numerous cases, on the contrary, no special local indication exists, and the question might arise whether here the selection of the seat of injection is entirely a matter of indifference, or whether it requires a certain amount of consideration and precaution. For even in such cases certain parts of the body must, more or less, unconditionally be often excluded, whilst others, on the contrary, may be considered as more suitable for the injection. Those generally to be avoided (under the limitation set by local indications) are the specially sensitive portions of the skin, abundant in nerves, and which have been found by experience to exhibit, on slight irritation, extensive reactionary effects, as ecchymosis, &c.; also those parts in which a very firm and tight connective tissue, free from fat, exists—a tissue which does not permit the skin to be raised in large folds; and, finally, those portions in which numerous large venous branches run superficially. On these grounds, the nose, the eyelid, the neighbourhood of the auricle, the front and sides of the neck, the axilla, the elbow and

fingers, the scrotum, &c., are in general less suitable for injections; and in certain cases many peculiar individual considerations may be required to be taken into account besides those mentioned. Of course when we desire the general action of the remedy, those portions of the body are as much as possible to be excluded in which absorption is rendered difficult or is prevented by existing local pathological affections, such as stasis, œdema, inflammation, extravasation, &c. Moreover, even under normal conditions, absorption does not seem to take place in all parts of the body with equal safety, rapidity, and precision. It is evident that the varying thickness and strength of the subcutaneous tissue, and the varying proportion of its veins, lymph vessels, &c., must exercise some influence. It is true that precise data as to the local differences which in this respect prevail among men are very difficult to procure; we can only here, as I shall show more particularly further on, regard the appearance of certain primary and easily determined symptoms of medicinal action as somewhat doubtful indications. The results of such experiments are somewhat contradictory on account of the numerous existing individual diversities; still they always prove with some certainty the superiority of certain portions of the skin, to which belong particularly the region of the cheeks and temples, and neck, the inner side of the upper arm and thigh, the epigastric and hypogastric regions, &c. From cosmetic consideration, injections in the face, especially at the temples, must be avoided in women with a very tender skin (though Von Graefe recommended them as being preferable, with special regard, it is true, to ophthalmic practice). So also the physician, when injecting into the extremities, will keep as far as possible from the course of the large vascular and nervous trunks at the inner side of the limbs, as well as from the joints. Finally, where immediate injection is necessitated, he will simply perform it on that part of the body which is most easily accessible, without previous exposure, even though in other respects it is inferior, as, for instance, the back of the hand and the neck.

Of special importance for practical therapeutics are the observations which refer to the *rapidity of absorption of the*

injected substances, the duration of their stay in the blood, and the nature and rapidity of their elimination, as also to the *local medicinal effect*, more or less prominently appearing along with the general one.

We can most easily convince ourselves of the uncommon rapidity with which absorption in subcutaneous injection takes place by experiments on animals with different toxic substances. Particularly striking in this respect are experiments with hydrocyanic acid. If about 0·5 c.cm. (8 mins.) of a 5 to 8 per cent. solution of hydrocyanic acid is injected under the skin of the back of a rabbit, the animal, as a rule, remains quiet from 10 to 25 seconds from the moment of the injection, then all at once falls on its side, is seized with violent general convulsions, with dilatation of the pupils and starting of the eyes, and scarcely half a minute elapses before pulse and respiration cease. I have, for sixteen years, in the course of each session's lectures shown this experiment, and never seen the effect, imposing in its suddenness, fail to appear with a good preparation of the acid ; indeed when a stronger solution (20 per cent.) of hydrocyanic acid is used, the convulsions may appear during the injection, so that it is scarcely possible to finish it. Of course the inference from this is not that the whole of the injected hydrocyanic acid, but that a sufficient quantity to produce symptoms of poisoning in such an overpowering way, is absorbed. The great rapidity and energy with which other poisons, especially vegetable ones, such as curara, strychnine, nicotine, &c., by subcutaneous injection cause the severe toxic effects peculiar to them, and finally death, is well known from innumerable experiments on animals, as is also the fact that, among these vegetable poisons, many deleteriously acting substances are found which are almost without action on some species of animals when administered internally in the ordinary way, as, for instance, curara on rabbits, while when they are hypodermically injected, no perceptible trace of the apparent 'immunity' of these species of animals is observable. This latter point, however, will occupy us further on in another connection. It is easy to conceive that the results obtained in man by observation of the first manifestations of the pharmacological or toxic action of the substance are less striking, as it is

almost always relatively small quantities of substances intended for therapeutic purposes, and which do not act in such a violent way, that are used; there is also an additional difficulty in the irregularity of the appearance and order of the first toxic phenomena and in the great individual diversity in sensibility to medicinal action, such as, for example, appears in a very prominent manner with the drug which is most used in a hypodermic form, viz. morphine. But, even though one takes account of all these circumstances, yet, in a large number of patients, the astonishingly early average appearance of certain relatively frequent pharmacological phenomena after injection of morphine, atropine, ergotine, apomorphine, &c., can easily be confirmed. After subcutaneous injection of 0·01 to 0·03 gramme (0·15 to 0·45 grain) of morphine, there may be observed very often, without the necessity of supposing a penetration of a large cutaneous vein, almost immediate heaviness in the limbs, lassitude, burning in the head, slowing of the pulse and respiration, and, in irritable individuals, restlessness, anxiety, giddiness, faintness, nausea and a tendency to vomit, and sometimes also a bitter or sour taste in the mouth; many patients complain of a peculiar feeling of tightness in the back of the head, others of a similar feeling in the throat or in the epigastric region, as the first regular symptom of the commencing medicinal action, which they experience after 1 to 3 minutes, or even earlier. There can be no question of self-deception here; for those who are habituated to the use of injections of morphine can very readily distinguish whether, instead of a solution of morphine, water has been injected, and whether, instead of the strong solution, a more diluted one, or instead of the usual dose a smaller one has been injected. So also after the injection of 0·001 to 0·003 gramme (0·015 to 0·045 grain) of atropine, in 2 to 3 minutes, or even earlier, there is felt a considerable quickening of the pulse rate, increased feeling of warmth in the head, sometimes also a feeling in the throat and stomach as if there were a tendency to vomit; comparatively early, in 10 to 15 minutes, the evident symptoms of the action of atropine—viz. dryness and soreness of the throat, mydriasis, &c.—become perceptible. After injections of ergotine (0·1 to 0·2 gramme, or 1·5 to 3 grains of the aqueous extract of ergot)

there follows in many cases almost immediately a decrease of the pulse rate, a contraction of the arteries, sometimes also a feeling of warmth and a slight elevation of temperature; in certain patients, sudden collapse, and the appearance of apoplectic or epileptic seizures, have been observed a few minutes after the injection of this drug. The hypodermic administration of 0·003 to 0·004 gramme (0·045 to 0·060 grain) of apomorphine has often, in the course of 3 to 5 minutes, resulted in vomiting, in many cases also with symptoms of collapse, giddiness, blanching of the skin, small intermittent pulse, &c. These examples might be increased and varied at pleasure, but it is sufficient for our purpose to have called to mind the effect of some of the drugs which are best known and most generally used for injections.

In order to procure from animals still more precise data as to the rapidity of the absorption of substances when subcutaneously injected as compared with their internal administration, I have endeavoured to directly detect them in the *circulating blood.* The choice of solid or fluid substances, suited for this purpose, is certainly very small, as, on the one hand, drugs which undergo decomposition at the seat of application or in the blood itself, and, on the other hand, toxic substances which considerably disturb the circulation, must be excluded; and, moreover, only such substances can be used as can be easily recognised in small quantities of blood, even when very largely diluted. The alkaloids and glucosides, as also the metallic salts, &c., which are chiefly used for subcutaneous injections, are entirely unsuited for this purpose. I found a suitable substance, however, in amygdalin, the soluble nitrogenous glucoside ($C_{20}H_{27}NO_{11}$) contained in bitter almonds, which in itself is not poisonous, but which, as is well known, in contact with the ferment (emulsin) of the sweet almond, at the temperature of the blood, takes up water and becomes split up into hydrocyanic acid, sugar, and oil of bitter almonds. A gramme of amygdalin yields in this way 0·06 gramme of hydrocyanic acid and 0·5 gramme of oil of bitter almonds, an extremely small trace of which is detectable by its smell. The experiments were made on rabbits in the following way. Before the subcutaneous or internal administration of the solution of amygdalin, the external jugular

vein of one side was exposed and opened, and the opening closed with a small spring clamp. Then 3 to 4 c.cm. of a solution of 0·1 gramme of amygdalin in 7·5 c.cm. of distilled water were either subcutaneously injected, or introduced into the stomach of the animal by a stomach tube. The testing for the amygdalin took place at intervals of half a minute after its administration in such a way that the clamp in the vein was removed, and a small quantity of blood from it was as hastily as possible collected in a glass vessel (watch glass) filled with a solution of emulsin and slightly warmed. After the necessary quantity of blood had dropped into the glass, the vein was immediately closed again. So long as the blood contained a sufficient quantity of amygdalin, the characteristic smell of oil of bitter almonds and hydrocyanic acid, on mixing the blood with the solution of emulsin, was perceptible. I found in these experiments that, *after the subcutaneous injection of the above-mentioned dose of amygdalin, the blood, to which some emulsin had been added, yielded, as a rule, a very distinct smell of hydrocyanic acid after the lapse of* 3 *to* 4 *minutes*, and that the reaction was most evident after about 10 to 12 minutes, whilst after 20 to 25 minutes it began gradually to diminish. *After the internal administration of an equal amount of amygdalin, on the contrary, a distinct reaction could in general never be attained before the lapse of* 15 *to* 20 *minutes*. From these earlier experiments, more recently repeated by me with like results, it does not follow as a matter of course that absorption has only begun in 3 to 4 or 15 to 20 minutes after the application, but rather, that it may be regarded as proved, that at that time so much amygdalin is accumulated in the blood that it can be distinctly detected by the test now under consideration. The result is therefore a double one—firstly, that absorption in subcutaneous injection generally proceeds with great rapidity and energy; and, secondly, it teaches us that *when the same substances are administered by the mouth it is only after* 15 *to* 20 *minutes that an accumulation of the drug takes place equal to that which happens in* 3 *to* 4 *minutes in the subcutaneous mode of administration.*

An indirect, but much more convenient method, and one which is suitable in a greater number of cases, for the purpose

of measuring the rapidity of absorption of drugs or poisons that have been administered, and the comparative duration of their stay in the circulation, is furnished by testing for the presence of the substances in the *secretions and excretions.*

By this method it can easily be proved that various substances detectable in the secretions (saliva, urine) appear in them, in the case of men and animals, much more quickly after subcutaneous injection than after administration by the mouth; the conclusion from which is that these substances are conveyed into the circulation from the subcutaneous tissue more quickly than from the stomach. Of experiments on animals which I made in this direction, I mention only those with solutions of iodide of potassium, or of iodine and iodide of potassium, ferrocyanide of potassium, and tannin. All these substances are easily recognisable in the urine; and they could frequently be detected after subcutaneous application in 4 to 5 minutes in the urine obtained from the animal by the catheter or by pressure on the bladder. On the contrary, after internal administration they were never recognisable earlier than in 10 to 18 minutes. Of greater interest, as regards the question now occupying us, are experiments on men, as, on account of the different nature of the organs of absorption, their identity in man and the higher animals can by no means be assumed as indisputable. Experiments with iodide of potassium and with corrosive sublimate have, however, led me to results entirely similar to those which I obtained from experiments on animals, since the presence of the salt in the urine after subcutaneous injection could always be detected earlier than after its internal administration. Yet I soon gave up this method, as it could not generally lead to very precise results, because it is not possible to obtain at very short intervals of time quantities of newly secreted urine and thus to ascertain the first appearance of the excretion. A better method for attaining this object was opened up by seeking the drug in the buccal secretion, especially that of the parotid gland. If, according to the method described by Eckhard and Ordenstein, two cannulæ are placed in the mouths of the stenonian ducts (which with most people can be done, after some practice, without any material difficulty), and if, in case of necessity, secretion is aided by

chewing movements, pressure, application of sapid substances to the dorsum of the tongue, &c., a sufficient quantity of secretion is, as a rule, obtained in order to be able to test the reaction of the drug every minute, and under certain circumstances even every half-minute. Of course, only substances can be used for this purpose which are known to pass into the parotid secretion (as iodide of potassium, and corrosive sublimate), and which, moreover, are easily recognisable even when much diluted. It may in many cases be advisable, instead of only the parotid saliva, to use the whole of the buccal secretion for investigation, by which the difficulties of catheterising the ductus stenonianus, as well as accidental disturbances of the parotid secretion, are entirely excluded, and a larger quantity of secretion, though more diluted, is obtained for testing.

The most suitable substance for experiments is iodide of potassium. That it passes into the parotid saliva as well as into the other secretions of the mouth I have proved by experiments in which the secretion from both stenonian ducts and the other secretions of the mouth were separately collected. The secretion was tested by means of fuming nitric acid and chloroform or a solution of starch. I experimented on seven persons, to whom, on account of syphilitic or scrofulous swellings of the glands, periosteal tumours, tophi, &c., iodide of potassium was being administered hypodermically, a syringeful of a solution of 1 to 6 in distilled water being injected each time (thus about 0·15 gramme, or 2 to 3 grains, of iodide of potassium per dose). On the whole, fifteen experiments were made: in these the first evidence of the presence of the iodide appeared twice after one minute, three times in the second minute, seven times in the third, and three times in the fifth; thus, in the whole number of cases, before the lapse of five minutes!

With regard to the slight differences, it appeared to me that they were perhaps caused by the selection of the seat of injection. The minimum of the time of the appearance of the salt was obtained by injections into the neck or the breast; the maximum, on the contrary, from injections in the thigh (in syphilitic tophi of the tibia). The result of control experiments with the internal administration of the same doses of the same drug was that, in six experiments, the first trace of

the salt was detected, once after 20 minutes, once after 25, three times after 30, once only after 35 minutes. Demarquay, who investigated, in a similar way, the relation of the application by the mouth to the application to the rectal and urogenital mucous membrane, as also to the respiratory apparatus, states that, after internal administration, he could sometimes detect the iodide of potassium in the saliva and urine after 9 to 15 minutes; but in these cases much larger doses (0 25 to 1 gramme, or 3·8 to 15·4 grains) were administered internally by him. After the administration of 0·05 gramme, or 0·77 grain, it was not detected in the urine. When absorbed by the mucous membrane of the rectum, Demarquay could detect it after 2 to 7 minutes in the saliva; by the respiratory apparatus (inhalation from the spray producer), after 5 to 6 minutes in the urine; by the urogenital mucous membrane (bladder, prepuce, vagina)—the elimination takes place much later and with more uncertainty. The inference from these experiments appears to be that, after subcutaneous injection of drugs, their passage into the urine not only occurs more rapidly than after ordinary internal administration, but also more rapidly than after rectal, vesical, and vaginal application and after inhalation.

In the same way as with iodide of potassium, I have also made experiments with corrosive sublimate on the rapidity of its elimination in the saliva after subcutaneous and after the usual internal administration. These experiments were undertaken on two persons suffering from secondary syphilis. Each single dose amounted to 0·005 to 0·01 gramme (0·077 to 0·15 grain) of the drug in an aqueous solution of 1 : 100. As a testing reagent, I used either metallic copper or stannous chloride, after the previous addition of nitric acid. These experiments did not in all cases lead to a satisfactory result, on account of the extremely small quantities of the substance with which I had to deal, and I therefore lay no special weight on them; yet they confirm in general the results obtained by experiments with iodide of potassium. Out of six injection experiments which afforded a decided reaction, the first detection of the iodide was made three times within the first five minutes, and within the following five minutes three times also. On the contrary,

after internal administration of a similar quantity of the salt, its passage into the saliva was never detectable within such a short time.

Closely allied to the demonstration I have offered of substances appearing more quickly in the secretions after subcutaneous injection than after internal administration, and that thus their elimination begins sooner, is the question whether the elimination also ends sooner, and thus whether the whole duration of the stay of the drug in the organism generally is shorter. This question is not without interest for the therapeutic application of subcutaneous injection; for, if answered in the affirmative, the conclusion would be admissible *that every single dose given hypodermically corresponds to a more intense but yet a more evanescent effect, and that a cumulative effect is more difficult to obtain, by this method of administration, from a succession of doses.*

The therapeutic observations on the use of various narcotic and other drugs, such as atropine, digitalin, strychnine, &c., do not at least contradict this conclusion. In order, however, to obtain more precise information, I endeavoured, in the case of easily detected substances, to fix the *moment of their disappearance from the secretions* (*urine, saliva*) *after subcutaneous and after internal administration.* In experiments on animals with this object I used chiefly ferrocyanide of potassium, but also iodine and iodide of potassium, and tannin. To several rabbits equal portions of ferrocyanide of potassium (10 c.cm. of an aqueous solution of 1 : 6) were administered, in some subcutaneously, in others by the mouth, and the urine at regular intervals was tested, after acidification, by means of ferric chloride. (As part of the ferrocyanide is converted into the ferridcyanide in the organism, it is advisable, in case a reaction is not attainable with ferric chloride, to endeavour to secure one with ferrous chloride.) *Hitherto it has constantly turned out that, after subcutaneous injection of ferrocyanide of potassium, its presence in the urine is always confined to the first* 24 *hours, and that, as a rule, the reaction after* 16 *to* 20 *hours is very feeble. Whereas, after internal administration of the same doses, the urine contained even on the second and third days tolerably large quantities, and even after* 72 *hours it*

showed unmistakable traces of the salt; indeed, about the end of the second and third days the reaction, as a rule, was strongest.

These results were confirmed by Czarlinski,[1] who worked at this subject under the direction of Landois. He also, after the internal administration of ferrocyanide of potassium, could detect it after, at least, 48 to 50 hours, in certain cases even after 80 hours, in the urine of the animals experimented on.

The experiments made on rabbits with a solution of iodide of potassium and with tannin yielded, also when lately repeated by me, precisely the same results. The time between the introduction of these drugs into the organism and the completion of their elimination by the urine is, according to these experiments, two or three times greater after internal than after subcutaneous administration, so that the rapidity of the elimination proceeds in an almost equal degree with the rapidity of absorption and the accumulation in the blood. I have made experiments of a similar kind on men, employing, as already mentioned, iodide of potassium, and using its detection in the saliva of the parotid, or in the mixed secretions of the mouth, as a means of testing the rapidity of its elimination. Though the differences here were less prominent and striking (which was really owing to the smaller doses), yet the results entirely coincided with those obtained from experiments on animals. In the whole 15 cases of hypodermic injection of iodide of potassium, it was still detectable in the saliva after 12 hours; in 14 after 18 hours, in 10 after 24 hours, and only in 2 cases after 36 hours, and it was not found in any case after that time. As regards its internal administration, in the whole 6 cases it could be detected in the saliva after 12 hours, in 5 cases after 24 hours, in 3 cases after 36 hours, and in 1 case after 48 hours. Thus, in the saliva, the elimination takes place decidedly more quickly after subcutaneous application, and though it begins earlier yet it also ends earlier than after internal administration. The importance of these results for therapeutic practice is self-evident. If we imagine the substances we have employed to be replaced by differently acting

[1] *Ueber die Resorptionsgeschwindigkeit und die Aufenthaltsdauer des Kaliumeisencyanür im thierischen Körper.* Dissertation. Greifswald, 1867.

drugs and poisons, the daily repeated introduction of these into the organism by the mouth must produce an important cumulative effect, because only a relatively small part of one dose is removed from the body before the next one is administered. In subcutaneous injection, on the contrary, such a cumulative effect cannot easily happen, because, by the time that a fresh dose is given, the elimination of the former one has already taken place pretty completely, and by this means the simultaneous presence of several individual doses in the circulation is rendered impossible. *We can thus by subcutaneous injection not only considerably increase the rapidity of absorption, and along with it the prompt and energetic action of each individual dose, but, at the same time also, with greater certainty prevent the often undesirable occurrence of cumulative effects after the necessary repetition of the medicine.*

The question previously suggested, whether, along with the general effect produced by absorption, a specific local effect from the subcutaneously injected substance also takes place, refers, in the sense now occupying us, only to a local effect on the activity of the nerves, such as may be produced by exciting or depressing medicines, as narcotics, acting either on the motor or sensory nerves in the neighbourhood of the seat of injection. This question, it is easy to see, is not only of theoretic but also of eminently practical interest. In an extremely large number of cases we wish, in the subcutaneous injection of narcotic and sedative medicines, &c., to combine a specific local action with the effects due to absorption. We would often give the former the preference, could it be obtained alone, especially where the object to be gained is the abatement of pain or the arrest of cramp, &c. Indeed, many applications of the hypodermic method that have been proposed rest really on the supposition of a specific local action (for instance, the recommendation of injections of opium for the production of local anæsthesia in minor operations). Since the hypodermic method became known, the large majority of the opinions expressed about it are more or less in favour of a specific local action, without regard to any other particulars than empiric observation of the local success in pathological irritative con-

ditions of the sensory or motor nerves, such as the curative action of narcotic injections in pain and convulsions. This local action, however, frequently does not show itself sooner than the effects dependent on absorption, and should therefore certainly be regarded as part of the general action of the medicine. In other cases, it is true, the characteristic effects of absorption are absent, whilst the effect on the pain and convulsions is nevertheless present; but even this circumstance does not furnish a decisive proof in favour of a specific local action. For, as we have already seen, absorption goes forward, after subcutaneous injection of a remedy, uncommonly quickly and energetically almost from the moment of injection. The objection raised by Ch. Hunter may therefore be well founded, and it may be that even the action perceptible at the locality of the injection is produced only through the circulation, and only represents a part of the general action, and that therefore the advantage of the hypodermic method really consists only in the easier, more rapid, and more complete accomplishment of the general action of the remedy.

In opposition to this objection, therapeutic experience teaches us that the locality of the injection, especially in those cases in which the drugs injected are morphine and similar substances, as in painful local affections, such as neuralgia, reflex convulsions, &c., is of unquestionable importance for success. A. Wood himself settled this point; and the statements of authors who have made specially numerous and exact observations in the domain of hypodermic therapeutics entirely coincide with his. Some important individual observations of this kind may be mentioned. Rynd remarks that in neuralgia the soothing action of the injection is the more certain, the nearer the injected fluid is brought to the affected part, i.e. the nerves. Semeleder recommends that injections should always be made in the neighbourhood of the painful part, and where possible, somewhat below it. If, in sciatica, instead of the local injection of morphine, a much larger dose of morphine was administered internally, the general narcotic action did indeed appear, but the local antalgic action was very far from doing so, notwithstanding the much larger dose. Von Graefe too lays great weight on using the exact locality in injections of mor-

phine—for instance, in reflex spasms (blepharospasm), in which the previous discovery of a possible point of pressure of the involved sensory nerves must guide us in the selection of the seat of injection. Similar observations I have myself made very frequently in neuralgia, reflex convulsions, and other painful or convulsive local affections. Especially instructive, in the demonstration of the localised character of antalgic action, are the cases of bilateral neuralgia and similar affections. Sommerbrodt, for instance, adduces in proof of the local action a case of bilateral sciatica in which the injections made on one side always resulted in the abatement of pain on the side of the injection, but not in the opposite limb. I have already communicated an entirely analogous case in the first edition of my 'Hypodermatische Injection'; it was that of a thoroughly trustworthy man, forty years of age, with double sciatica, where the injection made at the painful spot always resulted in complete analgesia on that side of two or three days' duration, whilst on the other side, after the general narcotic action had passed away, the pain immediately returned.

In diffuse reflex spasms also, especially in epilepsy of peripheral origin, eclampsia, traumatic tetanus, &c., the local benefit of narcotic injections often appears in a very prominent and striking way; for instance, in epilepsy, injections performed at the seat of the aura, or in the locality of the corresponding nerve trunk, alone afford relief. On account of the extended application which subcutaneous injections of morphine have found in the department of psychology for more than ten years, the experiences of psychologists have special weight in the decision of the above questions. Schüle, in whose establishment the curative treatment of the insane by injections of morphine received its methodical development, speaks as follows on this point:[1] 'A further advantage of subcutaneous injection over internal administration is the local anæsthetic action. And in so far as these peripheral pains have been found by experience to act an important part in the excitement of certain psychical paroxysms, local application in these particular cases effects incomparably more than administration by the mouth.' 'A

[1] *Handbuch der Geisteskrankheiten* (vol. xvi. of the *Handbuch der speciellen Pathologie und Therapie* of Von Ziemssen, Leipzig, 1878), p. 667.

patient, who had become maniacal after an injury to the head, was preserved from threatening paroxysms, *only* when subcutaneous injections were made in the nape of the neck.'

It is true, however, that therapeutic observation and experience still leave many a doubt with regard to the local action exercised by the remedy injected, as an absolutely certain criterion is not afforded by the therapeutic result alone. In the hope of obtaining such a criterion, I made experiments at the beginning of my investigation of hypodermic injection, in order to determine *in healthy persons, by direct observation, control experiments, and measurements, the decrease of sensibility in a part after the local injection of a narcotic alkaloid, as morphine, atropine, &c.* Observations on the tactile sense of the skin, made by Weber's method, are especially appropriate for this purpose. From earlier investigations of Lichtenfels, it is well known that, after the internal administration of narcotics, the whole tactile sense is lessened, and the diameter of the 'touch limit' (smallest limit in which two points applied to the skin can still be recognised as dual) becomes increased over the whole body. This was also observed by Südeckum after the hypodermic injection of morphine or atropine. In order to distinguish the local action, which we have now to consider, from the general one, I proceeded in the following way:—First, with one of Volkmann's æsthesiometers (in which the distance between the applied points could be precisely read off by means of a scale divided into millimetres), or with one of Sieveking's æsthesiometers, the diameter of the touch limit was measured at symmetrical portions of the skin of both halves of the body. Then the injection was made on one side, and afterwards, at corresponding intervals, the changes that had taken place in the diameter of the touch limit on both sides were carefully compared. Of course the portions of the skin used for the comparison must be absolutely identical, and the points of the æsthesiometer, on both sides, must be held in the same direction to the skin. In these measurements it was always proved that after injection of morphine or atropine on one side, the tactile sense in the vicinity of the seat of injection was considerably weakened at the time when, in the corresponding cutaneous region of the other side, no weakening of it, or only

a materially smaller one, was perceptible. If the changes in the diameter of the touch limit in one and the same part of the skin are diagrammatically represented in the form of a curve, this curve rises very quickly at the seat of the injection soon after the operation, reaches its maximum after a certain time, and then gradually falls, but remains, however, for a pretty long time above the abscissa. (The extent and duration of the rise, as well as the greater or less rapidity of the descent, vary, other things being equal, essentially according to the size of the dose injected.) On the corresponding part of the skin of the other side, on the contrary, there is sometimes no rise at all, sometimes a much feebler and later one, often only to be recognised coming into contact with the descending part of the first curve; sometimes even a primary fall to beneath the abscissa precedes this rise—i.e. there takes place here, instead of an enlargement, at first a diminution of the diameter of the touch limit, which appears to be caused by the primarily stimulating action of the narcotic on the sensory nerve centres, perhaps also by the recently detected tendency in the body to antagonistic bilateral equalisation of sensibility.

Pretty frequently at the same time there is observed *on the side of the injection*, after a longer or shorter action of the narcotic within certain limits, a subjective varying of statements, so that persons experimented on, with the points of the æsthesiometer at the same distance apart, nevertheless believe they perceive sometimes two points, sometimes only one. Such a zone of uncertain sensibility is found, it is true, as Volkmann in particular has shown, under physiological conditions also, almost everywhere; it is, however, then much smaller. While normally it amounts, as a rule, to 1 to $1\frac{1}{2}$ mm. (0·04 to 0·05 inch) it may, under the influence of the narcotic in the vicinity of the seat of injection, extend to 10 mm. and even more.

To describe additional experiments appears to me unnecessary; I refer my readers to my other publications on the subject, and only remark that lately the testing of the electro-cutaneous (faradic) sensibility gave me analogous results, though with less striking differences, in symmetrical portions of skin. The considerable extension of the touch limit at the seat of

injection was also lately confirmed by Schüle,[1] whose statements on the subject are, however, not quite clear.

At all events it is proved by this method that the lessening of the tactile sensibility at the seat of injection not only appears earlier, but is also more intense and enduring, than at the corresponding part of the other side. If the injection is made in a part of the body in which a sensory or mixed nerve trunk runs superficially under the skin, e.g. the peroneal nerve at the head of the fibula, the tactile sensibility is lowered, not only at the seat of injection, but in the whole region of the skin supplied by that nerve, although at the seat of injection in a much higher degree. From these experiments we have, as I believe, the proof that certain narcotics, such as morphine and atropine, apart from their general action, exercise also a specific local action on the sensory nerves in the vicinity of the seat of injection, by lowering relatively and absolutely the tactile sense, as well as the general feeling of the skin in the regions supplied by the nerves. Injections of distilled water gave no such results, nor did injections of strychnine, veratrine, and saponine ; but sometimes injections of 2 per cent. solutions of carbolic acid did, the local anæsthetic action of which is, however, certainly very small. It would appear then that the local lessening of the sensibility cannot altogether be ascribed to the mere locality of the injection, or to the puncture, or to the distension of the subcutaneous tissue by fluid, but that in fact there is also here a purely medicinal local action.

Against the theory of such a medicinal local action, Hilsmann and Jolly have lately expressed their opinions, on the ground of experiments made with morphine. Hilsmann, whose work, in the original, unfortunately I have not got by me, asserts that in repeating the above experiments he obtained negative results, as, after injections made in the arm, he could not detect a difference of sensibility from the corresponding part on the other side. Moreover Jolly, by another method of experiment, has sought to shake our belief in the local action of morphine, viz. *by comparative measurements of the changes in the blood pressure following the stimulation of the sciatic*

[1] Loc. cit. p. 118.

nerves in animals before and after subcutaneous injections of morphine. However, the evidence afforded by the latter experiments is still subject to much doubt; for in the increase of the arterial pressure, which is caused by stimulation of the sciatic nerves, we are considering a reflex phenomenon produced through spinal (lumbar) centres; the unaltered occurrence of reflexes would, however, not exclude the possibility of the excitability of the terminations of the cutaneous sensory nerves, and of the centripetal transmission of nerve power along the sensory tracts, being weakened in a way which considerably lessens the perception of tactile stimulation acting on the peripheral cutaneous nerve endings. Thus it is well known that morphine in itself may have the effect of changing the arterial pressure in men and animals; and indeed it appears, in animals, first to effect a passing increase of pressure, from vasomotor stimulation (Gscheidlen), which is followed by a stage of vascular dilatation and lowering of pressure. Wolff[1] also arrived at corresponding results in man on the ground of investigations with the aid of the sphygmograph, whilst, more recently, Witkowski,[2] on the other hand, has observed a small lowering of the blood pressure after every injection of morphine, which is in all probability to be ascribed to a dilatation of the vessels due to central causes. At all events this preliminary question is not yet sufficiently decided to make it possible to draw from the condition of the blood pressure in Jolly's experiments a certain conclusion with regard to the local action of morphine. Even in the most favourable circumstances it could only be proved by these experiments that the excitability and conductivity of the large nerve branches are not locally altered by injections of morphine, whilst, on the contrary, such a local action might yet take place on the peripheral cutaneous tactile nerve endings. I am at present occupied with experiments on the action of injections of morphine made directly into the paraneurotic connective tissue and the nerve sheath of the larger nerve trunks (sciatic) of animals, the results of which I intend to report hereafter.

[1] *Archiv für Psychiatrie und Nervenkrankheiten*, ii. p. 601.

[2] *Archiv für experimentelle Pathologie und Pharmakologie*, vii. (1877), 3rd part, p. 247.

It is of importance, besides the local action of injected narcotics on the sensory cutaneous nerve endings, or the sensory fibres of nerve trunks, to also investigate the possible *local action on the motor nerves.* *À priori* it appears at least not inconceivable that a specific local action of a stimulating or depressing nature might also take place on the motor fibres of the nerves or intramuscular nerve endings after injection. In support of this supposition certain therapeutic facts at least may be adduced. Thus, for instance, Demarquay, in traumatic trismus and tetanus, asserts that he has obtained particularly favourable results from direct 'intramuscular' injection of solutions of morphine into muscles in a state of cramp, as near as possible to the point of entrance of the nerves into the muscles. Also, with respect to curara, Gherini mentions, on the ground of a case of tetanus which had been cured, that curara injected directly into the tissue of a muscle accomplishes its relaxation quickly and permanently. Polli also recommends injection or inoculation into the muscular tissue itself; and Gualla, in spasm of the facial muscles, injected curara into the muscles of the cheek affected with spasm, with the best results. On the other hand, after the local subcutaneous injection of strychnine in paralysis, I have often seen the slighter toxic effects, a feeling of dragging and tension, tremors, twitchings, &c., appear first or even exclusively in the muscles supplied by the nerves or in the adjacent muscles. I would not, however, attach much importance to this circumstance, because after the internal administration of strychnine similar effects are sometimes also first noticed in the paralysed parts. In order to obtain more precise data for the decision of this question, I have endeavoured both in animals and in healthy and sick persons to detect the changes, effected by local injections of morphine or strychnine, in the faradic excitability in larger, superficially lying nerve branches (as the peroneal, ulnar, and facial). I have not, however, as I will presently show, notwithstanding numerous experiments, arrived at any satisfactory and consistent results.

For performing these experiments, I made use of one of Du Bois Reymond's sliding induction coils, with a scale divided into millimetres. Before injection, the distance between the coils was ascertained, which, with indirect unipolar stimulation,

applied with the negative electrode, would produce a minimal contraction. After having thus ascertained the minimum of stimulus for the muscles of various nerve regions, as also for symmetrical nerve areas in both halves of the body, the injection was performed as much as possible in the vicinity of one of the motor nerves to be tested, or of the nerve to be used for stimulation, or a superficially situated nerve trunk, and then at periodic intervals the faradic irritability of the nerve used for injection, as also of the other selected nerves, was again compared as before. The results, as already mentioned, were very indefinite and contradictory. For instance, after injections of strychnine into the neighbourhood of superficial nerves, as the peroneal, the excitability was evidently sometimes increased in certain of the muscles which the nerve supplied, while in others it was quite unchanged. The increase of excitability was, however, scarcely greater than the simultaneous increase that could be detected in the muscles supplied by other nerves, as the tibial, or remote nerve trunks (obturator, crural), so that I could not infer that a local increase of excitability was produced by the strychnine. Just as little could I say that a local diminution of excitability was produced by morphine in this way It would indeed be over hasty to attempt to infer from the doubtful or negative results of these experiments that injected alkaloids have generally no specific action on the motor nerves. The solution of alkaloid, which reaches the nerve through the surrounding cellular tissue, may possibly be too much diluted to produce in its motor fibres, in proportion to the amount of the general effect, any distinct change of excitability; while the sensory fibres of the same nerve are perhaps subject to a perceptible and measurable local influence. Experiments on the exposed and excised nerves of animals afford proof that a local exciting or depressing action on the motor nerve fibres and terminations is produced by numerous substances, if these are directly applied in suitable proportions, sufficient concentration, &c. This appears also to be partly the case in direct injections of solutions of alkaloids on or under the perineurium of the larger nerve trunks, such as the sciatic; but this is certainly a proceeding which we could make use of in men only in exceptional cases, and which besides could be no

longer ranked with the subcutaneous injection of medicine in its usual sense.

We have now shortly to consider the *relation* in which the *subcutaneous application* of medicine stands to *other methods* of administration, especially to the usual internal administration, from which at the same time the general indications for the use of the hypodermic method will easily be inferred. We may leave out of consideration all comparison with the methods of epidermic and endermic application; since, so far as these methods, as well as those of inoculation and implantation, have to do with a general action produced by absorption, they can hardly at the present day, for the reasons already discussed, be regarded as rivals of subcutaneous injection, and except in rare, exceptional cases have been entirely expelled from therapeutic practice by the latter method.

The case is, of course, entirely different with the internal administration of medicine in its narrower sense—its administration by the mouth—though certain great enthusiasts, such as in general never fail to arise when new acquisitions are made in the domain of medicine, have even temporarily dreamed of its universal abrogation and the substitution of the hypodermic method in its place. The simplest consideration, however, at once proves that hypodermic injection, though suited for very many cases, is still a method which forms the *exception* and not the rule in the administration of drugs. If, however, the latter method possesses undeniable and even extremely important, and, within its own narrow territory, invaluable, advantages, yet with these are combined manifold disadvantages, which essentially restrict its use, and which entirely exclude it from by far the greater half of the sphere of therapeutics. These disadvantages consist above all in the restrictions which the nature of the method makes with regard to choice, form, and dose of the remedy; as also in the frequently undesirable intensity of the action, in its many kinds of subjective inconveniences and discomforts, and in the abuse to which it is liable equally among physicians and the laity. Although in a given case only some of these disadvantages are either noticeable, or far exceed the others in weight and importance, yet they all con-

tribute to limit the extent of usefulness of the hypodermic injection, and to oppose to its employment many contra-indications, even when it is used according to the generally recognised indications.

The *choice of drugs* to be injected is restricted as follows. Except certain special indications be present, all those medicinal preparations must be excluded which may give rise to violent or destructive local changes of the tissues; as also all those preparations which are quite insoluble, or which are soluble only in very large quantities of fluid or in strongly irritating fluids; and, finally, those which are efficient only in considerable doses of the drug, and where a correspondingly large quantity of fluid is necessary. On the whole, therefore, injection is specially suitable only for non-irritating, non-corroding substances, which are tolerably soluble in indifferent fluids (water, or glycerine), and the efficient amount of whose solutions on an average never exceeds a gramme (15½ minims). For the same reasons, the employment of most inorganic drugs is almost entirely forbidden, especially the greater number and the most important of the salts of the metals, the acids, alkalies, &c.; as also the employment of numerous vegetable remedies, whose irritating action on the skin, or difficult solubility, or largeness of therapeutic dose presents a difficulty, as, for example, the ethereal oils, most of the resins and balsams, and most of the substances reckoned in the class of the 'acria.' In practice, the selection is reduced in the main to a group of active medicines, chiefly belonging to the class of narcotics, and even of these as a rule we can only use their isolated active principles (narcotic alkaloids and glucosides). Though these, by reason of their conspicuous action and relatively small dose, appear to be peculiarly suited for subcutaneous injection in general, yet here also in individual cases manifold difficulties present themselves, which are caused by the insufficient purity and varying quality and activity of these preparations, their difficult solubility, deficient or uncertain knowledge of their pharmacodynamic and toxic properties, partly also their high price and the difficulty of obtaining them. Thus, for instance, it is at present extremely difficult, if not almost quite impossible, to get from druggists a chemically pure crystallised preparation

of hyoscyamine or digitalin, possessed of distinct pharmacodynamic properties. As is only too natural with the varying qualities of such preparations, opinions and experiences as to their therapeutic properties are widely different; indeed, they even stand in almost irreconcilable contradiction (as, for instance, with regard to the antipyretic action of digitalin). Everyone, however, who has made a large number of observations on this matter will at once confess that the precise and certain action which we obtain by the ordinary internal administration of digitalis in suitable cases has not hitherto been obtained by the subcutaneous injection at least of our German preparation of digitalin, and that therefore it seems scarcely warrantable in the meantime to seek in the hypodermic method a substitute for the internal administration of this important remedy. Nor is the case very different with colchicine, 'German' aconitine, and physostigmine, the supposed producers of the action of colchicum, aconite, and the Calabar bean. Chemically pure curarine is at present not to be got with certainty; the subcutaneous application of curara, however, must of course be confined to exceptional cases and conditions in which the strictest control and superintendence can be exercised, on account of the extraordinary inequality and diversity of action of this drug. The high price, apart from other considerations, forms an essential hindrance to the more extensive application of many substances belonging to this department, such as curarine, eserine, muscarine, duboisine, &c. These examples cannot but show how in the meantime, even with a peculiarly suitable class of remedies, their hypodermic use is still subject to numerous hindrances and restrictions, many of which, it is true, may undoubtedly be regarded as likely to be removed in the future.

The circumstance that a remedy often acts with unusual violence after its injection subcutaneously, and therefore gives rise to symptoms of poisoning and other disquieting phenomena, prejudices this method of administering it, especially in private practice, where the patient cannot always be watched narrowly and constantly after the injection. Apart from the fact that for this reason many therapeutically active remedies, and which are otherwise very suitable for hypodermic injection (e.g. atropine), are not very popular, such a bad result

as above described may be to a certain extent obviated, at any rate in the case of the drugs which are most relied on and most frequently used by physicians for injection. For this purpose we ought always, when treating patients whose individual sensitiveness is not sufficiently well known from earlier experiences, to begin with the minimum injection dose, and, in addition to this, to warn them beforehand of the possibility of somewhat disquieting phenomena making their appearance, as, e.g., vomiting after injection of morphine. Further disadvantages of this method are the pain connected with its performance, which, though as a rule slight, is still rarely entirely absent, the possibility of bad local symptoms, and the disinclination of many patients to it, a disinclination which arises from very various motives—the fear of the wound, prejudice, &c. Patients who are much afraid of the sight of blood or a wound have at first a certain amount of fear or aversion to hypodermic injection, because of the operative procedure that is combined with it. This, however, as a rule vanishes after the first few experiences of the smallness of the puncture, and the favourable curative or palliative effect of it. At the time of the gradual introduction of this method of treatment the mistrust of this new, strange, and mysterious operation, which was also performed by physicians with much less certainty and adroitness than it is now, was much more common and widespread. Nowadays this negative difficulty of novelty is gone; thanks to the untiring efforts at popularising of the present day and to the ever more and more astonishing penetration of medical knowledge amongst the laity, all classes of the public are sufficiently—often indeed more than sufficiently—educated as to the value of the method under consideration. For indeed it happens to the physician nowadays that other objections and scruples against treatment by injection—e.g. the merely temporary effect of injections of morphine, and the danger of some injury to the whole organism being produced by this mode of giving it—are made by the patient or his friends. It has not been absolutely advantageous to the reputation of treatment by injection in general that, at any rate in Germany, the hypodermic use of *one* remedy (morphine) has been almost exclusively cultivated by the majority of physicians, and has been made the only standard of the

value of the whole method in the eyes of the public. The abuses which the subcutaneous use of morphine, otherwise such an important and successful therapeutic measure, bears in its train, abuses which in our day culminate in the peculiar and apparently ever spreading morphine habit (*Morphiumsucht*), or morphiophilism, must have contributed their share to discrediting the hypodermic method in the estimation of physicians and the laity. The reputation of the operation must also have been greatly injured by the circumstance that the performance of hypodermic injection is now no longer looked on as the duty of the physician alone, but that it is done by nurses, then by the laity of all sorts, and lastly even by the patient and his friends, in some cases without the knowledge of a physician, in others however with his permission, given for the sake of convenience.[1] Now although these things are much to be complained of, still on the other hand we must not over-rate their importance, and in instituting a comparison between different methods we must not forget that the usual internal administration of drugs is open to similar abuses, which are even more frequent and widespread. Apart from opium-eating, we need only remember the habitual use of chloral, which is so extensive in England and America, the arsenic eaters of Styria, &c.

As against the disadvantages and evils of the hypodermic method which have been described, let us now consider the advantages which it possesses over the internal administration of drugs. These are of very various kinds, and are in some measure apparent from our former considerations. Especially must we remember the more rapid and energetic appearance of the general action produced by absorption, and the therapeutic effect dependent on this; also the combination of the general action with a desired local medicinal effect. But, apart from this, the hypodermic method is applicable in a large series of cases in which the internal administration of drugs is unsuitable, or contra-indicated by special conditions, or is rendered difficult or even impossible. To those cases in which *cæteris*

[1] We are so advanced in this matter nowadays that already speculative laymen have pirated this theme in their own way. Vide *Die Morphiumeinspritzungen, sicherer Führer für Aerzte und Laien*, by Paul Altvater, 2nd edition, 1879.

paribus drugs may be advantageously used hypodermically in preference to being administered by the mouth—except when we wish to combat locally some existing affection of the digestive apparatus—belong numerous diseases of the digestive system, especially those which are accompanied by great abnormalities of structure and secretion, with corresponding disturbances of function, and in which, therefore, we have to expect defective and imperfect absorption on the one hand, and irritation of the affected mucous membrane and increase and aggravation of the existing local processes from internal medication on the other. In this category must be placed, among others, conditions of obstinate inclination to vomit, of gastric irritability of pregnant and parturient women, of vomiting and diarrhœa, cholera, &c. Further, we must add those cases also in which exist purely mechanical hindrances to the administration of drugs by the mouth, due either to their entrance into the stomach being prevented by local diseases of the upper part of the digestive tract—such as severe tonsillitis, foreign bodies, and stenosis of the œsophagus and cardiac end of the stomach—or to attempts at swallowing and gulping, reflexly causing dangerous paroxysms, tetanus, local cramps, or general convulsions, as in hydrophobia and acute maniacal delirium; or, finally, to the patient obstinately refusing to submit to internal medication, as is not rarely the case in patients suffering from mental disturbances, as melancholia with suspicion of poisoning, &c., where food is often also refused. We must further take into consideration the circumstance that there are remedies which only produce their characteristic general action with difficulty and imperfectly, or indeed not at all, when applied to the mucous membrane of the digestive tract, either because there are some special hindrances to their absorption from the stomach or intestine, or because the secretions of the digestive organs so alter their properties as to militate against their physiological action. Experimental observation teaches us that in many classes of animals there exists a peculiar tolerance of certain poisons, which almost amounts to total immunity, especially when they are administered internally; and this condition must apparently be considered to be caused to some extent by some specific structural peculiari-

ties of the digestive apparatus, or by the composition of the digestive secretions in these classes of animals. As examples, we may refer to the tolerance of rabbits and other herbivora for curara and aconitine, of many species of birds for opium and its alkaloids. In man, curara and its alkaloid, curarine, are only absorbed from the stomach slowly and with difficulty, whilst their activity when administered externally, either endermically or hypodermically, is undoubted. We find an analogy to this fact in the harmlessness of certain pathogenic substances or poisons producing specific diseases, especially organised contagia, when they come into contact with the mucous membrane of the digestive tract; while, on the other hand, the entrance of the smallest quantity of these substances into a wound of the skin, or directly into the capillaries and veins, is sufficient to call forth symptoms of severe disease and even dangerous general infection, all of which has been repeatedly confirmed by recent investigations.

As further, though less important, advantages of the subcutaneous over the internal application of drugs, we may mention that, by the use of the former, the production of cumulative effects, which are often so undesirable, can be much more easily guarded against, on account of the more rapid elimination of the separate doses taken; also that the disagreeable taste of drugs, and the repugnance which children especially feel to taking medicine on account of this bad taste, or indeed to taking medicine at all, and which we have to combat, is obviated; and, finally, that very much smaller single doses of a remedy, and therefore a much smaller total amount of it, are needed, which, when we are using costly drugs (e.g. quinine), is of some importance, especially in hospital or dispensary practice.

Briefly, we may say that *the subcutaneous administration of drugs*, so far as they are suited for this method, *must be preferred to their administration by the mouth under the following circumstances*:—

1. *In cases where we wish to produce as rapid and as energetic a general medicinal effect as possible by increased rapidity of absorption of the drug, as in acute cases of poisoning, imminent suffocation, internal hæmorrhages, threatening collapse, or in severe disturbances of innervation and in*

general diseases which come on in paroxysms, as in neuralgia, convulsive seizures, asthmatic attacks, and intermittent fever.

2. *In cases where we wish to combine a specific local medicinal action, especially on the sensory or motor nerves, with the general one, as in painful local affections of very various kinds, neuralgia, reflex spasms.*

3. *In cases where internal medication is contra-indicated, hindered, or rendered impossible, as in psychical diseases, and in mechanical obstruction in the upper parts of the digestive apparatus, or organic disease, structural alterations, or serious functional abnormalities of it; or where we wish to use a drug which produces its general action only imperfectly and with difficulty when applied to the gastro-intestinal mucous membrane.*

It is very difficult to determine beforehand what substances are exactly suitable for subcutaneous administration. The number of organic and inorganic drugs and preparations which have been used to a greater or less extent in this way is indeed very large. Of these, however, there are many which are entirely useless, others that are at least superfluous and that may be easily replaced by better remedies; others, again, that ought to be used only in exceptional cases, especially where local irritation, or alteration and destruction of tissue, is permissible or is desired, and which, therefore, belong on the whole more to the domain of interstitial and parenchymatous injection. On the other hand it is to a high degree probable that the number of drugs fitted for subcutaneous use would be enriched by many that are new and valuable, if we could succeed in isolating the active principles of both old and new crude drugs, in the form of substances chemically pure and suitable for hypodermic injection, or if by proper pharmaceutical preparation we could render some other well-known remedies fit for this method of administration.

I shall in the following pages describe in their order the remedies which it has been proposed to use, and those which are actually being used subcutaneously, and, when treating of the more important of them, I shall add a few short directions and hints, which are based on my experience of them in practice,

as to their form and dose, &c., without going into any discussion of a pharmacodynamic or therapeutic nature of the individual remedies, which can be found in the text-books of materia medica and therapeutics. With reference to the classification, I may remark that I have sought to keep closely to that of Falck,[1] which I look upon as the only good chemical classification of drugs in accordance with the present time, and which I have of late made the foundation of my lectures on materia medica, so far as I could do so without confusion. By far the greater number of the substances which we shall have to take up are *organic*, and especially organic bases and glucosides; further, also organic acids, alcohols and their derivatives, and æthereal oils and allied vegetable and animal substances. The *inorganic* remedies constitute the minority of those which are used hypodermically; they are various metalloids, inorganic acids, and preparations of the metals.

ORGANIC REMEDIES.

Opium and its Alkaloids (*Morphine*, *Codeine*, *Narceine*, *Papaverine*, *Thebaïne*, *Narcotine*, *Apomorphine*).

Opium.—Opium has been used hypodermically simply dissolved in water, and also as the tincture and extract. Tincture of opium,[2] as well as the aqueous extract of the German pharmacopœia, may be used—the former, without water, in a dose of 0·25 to 1 c.cm. (4 to 15 mins.); the latter, dissolved in an equal part or more of water, in a dose of 0·03 to 0·1 gramme ($\frac{1}{2}$ to $1\frac{1}{2}$ grains). I have often used these two preparations subcutaneously, but they possess no advantage over the alkaloids, and therefore I consider them as quite unnecessary for hypodermic use. Powdered opium is permissible at most in carefully filtered aqueous solution, but has nothing to recommend it.

Morphine.—Pure morphine is not used, on account of its being so difficultly soluble; its salts alone are employed, as the acetate, hydrochlorate, and sulphate, which are officinal in Germany. Acetate of morphine is richest in pure alkaloid, containing 86 per cent., while the hydrochlorate contains 80

[1] *Uebersicht der Normalgaben der Arzneimittel u.s.w.* Marburg, 1875.

[2] [The English tincture (1 : 13) is weaker than the German (1 : 10).—TRANSL.]

per cent. and the sulphate 76 per cent. These differences are, however, in this connection not considerable. What is of more importance is the difference in solubility, at any rate as far as aqueous solutions are concerned. The most soluble is the sulphate, which we do not use very often; it is said to be soluble in 10 parts, or even less, of water (which, however, I have not been able always to confirm); the hydrochlorate dissolves in 20 parts, and the acetate, with a little acetic acid added to it, in about 24 parts. We should therefore advise as most suitable a 5 per cent. solution of the hydrochlorate in distilled water, or an acidified 4 per cent. solution of the acetate. The latter solution, however, on account of the addition of the acid, is more painful, and is subject to a fairly rapid decomposition and partial separation of the morphine salt, owing to gradual evaporation of the acid. Stronger concentrations of an aqueous solution are naturally not suitable. It is to be remembered that all aqueous solutions of morphine have this disadvantage, that they allow fungi to grow in them, and therefore cannot be kept for a long time. The growth of fungi can, however, be prevented by the addition of a small amount of chloral hydrate or of aqua laurocerasi (Dujardin-Beaumetz); such additions, however, are apt to interfere with the action of the drug, and they are not in all cases sufficient. Apparently carbolic or salicylic acid in very small quantity is better, as we see in the case of preserving solutions of ergotine. [The addition of salicylic acid to the extent of one per cent. of the morphine does not appear to prevent decomposition.—TRANSL.]

The practice which is recommended by many pharmaceutists, and even here and there by physicians, of warming and purifying by filtration turbid solutions of morphine which are in a state of decomposition, or in which the salt has become precipitated from its solution, is in no way advisable. Even though we may, by simple filtration, get a solution which is locally non-irritating and harmless, still we cannot accurately estimate the amount of morphine in the filtrate, and therefore it has an unequal and uncertain action. Moreover, if we immediately use for injection the fluid which has been warmed, or warmed and filtered, a part of the morphine salt may be precipitated by cooling during the filtration or during the injection,

which is decidedly to be avoided. We must therefore adhere to the rule, that *a solution of morphine which has once become turbid and is decomposing and throwing down the salt must not be used for injection under any circumstances.* It is much better (as I have done for nearly fifteen years) to dissolve the morphine salt, which is to be used hypodermically, not in water, but in chemically pure glycerine, and afterwards, when the injection is to be made, to dilute this solution with an equal quantity of distilled water. It is better for us to prepare our own solutions of morphine, since we cannot always depend on obtaining them equally and properly prepared by the druggist. Acetate and hydrochlorate of morphine dissolve on heating in 5 parts of glycerine; but it is better to make a solution of the strength of 1 in 10, by warming over the spirit lamp 1 part of the salt with 10 of glycerine placed in a test tube. Such a solution is quite clear, yellow or yellowish-brown in colour, and does not become turbid even on standing for several months, and, if pure glycerine has been used, no fungus will grow in it. To this solution we may add an equal quantity of water.

℞ Morphiæ hydrochloratis	1 gram. (15 grains)
Glycerini puri	10 c.cm. (150 mins.)
Calefac. et solutioni perfectæ adde	
Aq. dest.	10 c.cm. (150 mins.)

We thus obtain a solution of 1 in 20, of which 0·1 to 0·6 c.cm., or 1 to 10 mins. (0·005 to 0·03 gramme, or $\frac{1}{20}$ to $\frac{1}{2}$ grain, of morph. hydrochlor.) would be the usual single dose.

Fig. 4.

Another way in which we may administer morphine and other similar substances subcutaneously, but which up to the present has not been used very much in Germany, is by means of *gelatine discs*, as suggested by Sansom, and which, under the name of 'patent hypodermic remedies,' are specially well prepared by Savory and Moore, of London. They are small, extremely thin, square discs of about $\frac{1}{3}$ of an inch square, 24 of which are contained in a glass tube, which is inserted into a small wooden box (fig. 4). Each of these discs contains 0·01 gramme of morphine, and is quite soluble in a few drops of warm water; and, as I have convinced myself, they may be kept for years without

deteriorating, and they are much more convenient for the physician to carry with him than the usual morphine solution.

Codeine is not used much, and we can quite well do without it. For injection, it is dissolved in dilute hydrochloric acid, or a one per cent. solution of hydrochlorate of codeine is used, the dose being twice as much as that of morphine. Discs are made containing 0·015 gramme ($\frac{1}{4}$ grain).

Narceine is dear and not suitable for hypodermic injection on account of the difficulty of dissolving it; its therapeutic advantages over morphine are very doubtful. We must dissolve the alkaloid in dilute hydrochloric acid; the solution, however, very soon decomposes, and the narceine partly separates out. Dose, two or three times that of morphine (up to 0·08 gramme or $1\frac{1}{4}$ grain). A combination of morphine and narceine has been recommended; 1 gramme morph. hydrochlor. in 20 grammes water, with 1 to 2 c.cm. of a 10 per cent. solution of narceine (Lubanski). The advantage of this is very doubtful.

Papaverine, which is of very dubious value as a hypnotic, has been lately used subcutaneously in the treatment of mental diseases (Leidesdorf, Schüle). It is soluble in dilute hydrochloric acid, and the dose of it is the same as that of morphine.

Thebaïne and *narcotine*, which are the stimulating alkaloids of opium, are quite worthless for hypodermic as they are for any therapeutic use. As to laudanosine, which has lately been investigated by Falck, we have no experience of it.

Apomorphine, on the other hand, is much used as an emetic and expectorant, and most frequently in the form of subcutaneous injections. The best preparation for our purpose is the hydrochlorate (amorphous or crystalline), which is usually dissolved in water, 1 to 100; such a solution often, however, becomes turbid, owing to a partial separation of the salt, so that a still greater dilution may be necessary. The dose of the above solution is, as an emetic, 0·3 to 0·8 c.cm. (5 to 12 mins.), = 0·003 to 0·008 gramme of apomorph. hydrochlor., for adults, and 0·1 to 0·15 c.cm. ($1\frac{1}{2}$ to $2\frac{1}{2}$ mins.) of solution, = 0·001 to 0·0015 gramme of the salt, for children; as an expectorant, a less dose must be given. [The dose, to begin with, should be small, and let it be repeated if it fails to act. A dose of 10 mgrms. produces in many persons very violent symptoms.—TRANSL.]

Rabon injected as much as 0·01 gramme ($\frac{1}{7}$ grain) in the case of an insane person, but found that even after 0·003 to 0·004 gramme ($\frac{1}{20}$ grain) of the salt sudden collapse was apt to ensue (similar symptoms of collapse have also been observed by Prevost and others, only exceptionally, however). We may also use Savory and Moore's hypodermic discs, containing 0·006 gramme ($\frac{1}{10}$ grain) of apomorphine. The English preparation appears to be stronger than the German.

Belladonna; Atropine.

The *extract of belladonna* is used now and then, but it is not to be recommended on account of the liability to the formation of an abscess at the seat of puncture.

Atropine is not used in the form of the pure alkaloid, which is extremely insoluble, but in that of its salts, and in Germany almost entirely in the form of the officinal *sulphate*; exceptionally also the *valerianate*. Since the dose for injection is very small (on account of the ease with which toxic effects ensue), we do well to use a very dilute solution, 1 in 500, and of this to take 0·5 to 1 c.cm. (7 to 15 mins.), = 0·001 to 0·002 gramme ($\frac{1}{60}$ to $\frac{1}{30}$ grain) of the salt, as an average dose, and the same quantity of the valerianate. [A much larger dose (0·005 to 0·010 gramme) can be safely given as an antidote in cases of morphine poisoning.—Transl.] We can also get gelatine discs, each containing 0·0005 gramme ($\frac{1}{120}$ grain). *Combined solutions of morphine and atropine* have been much recommended, since they are said to prevent the toxic effects of both drugs, especially the vomiting after morphine, and yet to modify in no way the general action of both, except it be to increase it; I have, however, not been able to confirm this statement. Nussbaum mixes together 0·01 gramme of morphine and 0·001 gramme of atropine, Fraigniaud 0·05 gramme of morphine and 0·0025 gramme of atropine; Lubanski recommends a solution of morphine of 1 gramme in 20 c.cm., with 1 c.cm. of a solution of atropine (1 to 1000). Some physicians have combined the morphine-atropine injections with subsequent chloroform inhalations (E. Fränkel, Kleinwächter—in after-pains, tetanus uteri). Gelatine discs are made contain-

ing 0·01 gramme ($\frac{1}{6}$ grain) of morphine and 0·0005 gramme ($\frac{1}{120}$ grain) of atropine.

Stramonium; Daturine.

Extract of stramonium, and *daturine* (which, according to Von Planta, is identical with atropine, but according to later investigations by Pöhl[1] is chemically different), are separately used for injections, the latter, in aqueous solution with the addition of sulphuric acid, in a dose not exceeding 0·001 gramme ($\frac{1}{60}$ grain); but it is scarcely to be recommended. Discs of 0·0005 gramme ($\frac{1}{120}$ grain) may be also used. [The most recent investigations appear to show that daturine is a mixture of two alkaloids, one of which is identical with atropine, and the other with hyoscyamine.—Transl.]

Duboisia; Duboisine.

The alkaloid, which is very similar to atropine, but is apparently more active, is contained in the extract of *duboisia myoporoides*, and has lately been used subcutaneously by Ringer, Gubler, and myself. Schering's preparation ('sulfate neutre de duboisine') in aqueous solution, in a dose not exceeding 0·0005 to 0·001 gramme ($\frac{1}{120}$ to $\frac{1}{60}$ grain), appears to act as strongly as twice that dose of atropine would. It is at present very dear, costing forty shillings for 1 gramme.

Hyoscyamus; Hyoscyamine.

Tinct. hyoscyami and *hyoscyamine* have both been used hypodermically. The latter up to the present is difficult to get in a crystalline form,[2] and the non-crystalline fluid preparation is apparently of very unequal action, and therefore not recommendable.[3] The form and dose are very similar to those of atropine (according to Sydney Pearse, 0·001 gramme to 0·0015 gramme, or $\frac{1}{60}$ to $\frac{1}{40}$ grain); Pitha says that he injected 0·006

[1] *Petersburg. med. Wochenschrift*, 1877, 20.

[2] Lately Schuchardt has prepared it at 19*s*. per gramme.

[3] [Hyoscyamus contains two alkaloids, hyoscyamine and hyoscine. Both are crystallisable, and have a similar action to atropine, but the first is only half as powerful, while the second is fully as powerful as atropine.—Transl.]

gramme into himself and almost immediately became unconscious).

Calabar Bean; Physostigmine (Eserine).

Extract of Calabar bean, especially in solution in glycerine (1 to 60 according to M. Rosenthal), has been used for subcutaneous injection, also in aqueous solution (0·15 gramme to 4 grammes aq. dest., given by Eschenburg in a dose of 1 to 5 minims in Trismus neonatorum); also the principal alkaloid of the Calabar bean, *physostigmine* (*eserine*), under which name indeed preparations of very unequal value are sold, and which are to a greater or less extent adulterated with calabarine, an alkaloid which has a similar action to strychnine, according to the recent researches of Harnack. Physostigmine, or eserine, in watery solution with the addition of hydrochloric acid, or as hydrochlorate or sulphate of physostigmine, may be given in the same doses as atropine (Bouchut[1] has recently used it in chorea in doses up to 0·005 gramme, or $\frac{1}{14}$ grain); or Savory's gelatine discs, which contain 0·01 gramme ($\frac{1}{6}$ grain) of the extract of Calabar bean, may be used.

Nux Vomica; Strychnine.

Tincture of nux vomica was used by Luton, who injected as much as 5 c.cm. (80 mins.) in 24 hours in the agony of suffocative catarrh, &c.; locally, simple swelling and redness is said to have followed, but this disappeared in one or two hours.

Strychnine.—We do not use the pure alkaloid, but the salts, and in Germany especially the officinal nitrate, also, however, the sulphate, chloride, and acetate, all in aqueous solution (1 to 100), and in a dose of 0·3 to 0·6 c.cm. (5 to 10 mins.) of this solution = 0·003 to 0·006 gramme ($\frac{1}{20}$ to $\frac{1}{10}$ grain) of the salt; or in discs containing 0·001 gramme ($\frac{1}{60}$ grain). [The sulphate is more soluble than the nitrate, and, therefore, perhaps preferable for subcutaneous injection.—TRANSL.]

Coffee; Caffeine.

Garrison injected a strong *decoction of coffee* in a case of morphine poisoning. *Caffeine* is more often used; solutions of

[1] *Bull. gén. de thérapeutique*, 1875, No. 4.

it which have been prepared with acids (sulphuric, hydrochloric, acetic, and citric) become decomposed with tolerable rapidity, so that the drug on the whole appears to be unsuitable for hypodermic use. [The simple salts of caffeine are somewhat insoluble, as well as liable to decomposition in solution. Some of its double salts are, however, freely soluble, and those prepared with benzoic or salicylic acid keep admirably. Riegel gives the following formulæ (taken from Tanret), which he has employed with good results in heart disease. He advises a dose of 0·4 to 1·0 gramme (6 to 15 grains):—

℞ Caffein. . . .	2·5 grms.	℞ Caffein. . . .	4·0 grms.
Sod. benz. . .	2·95 „	Sod. salicyl. . .	3·10 „
Aq. ad . . .	210 c.cm.	Aq. ad . . .	210 c.cm.

—Transl.] Besides *citrate* of caffeine, which we are accustomed to use, the *hydrobromate* also has been recommended by Gubler and Féréol[1] as a diuretic. The dose of caffeine is 0·01 to 0·03 gramme ($\frac{1}{6}$ to $\frac{1}{2}$ grain) and even more. Gelatine discs contain 0·03 gramme ($\frac{1}{2}$ grain).

Aconitine.

Under this name we find preparations which differ largely in the extent and the character of their action; it is sufficient to compare the much more intense local and general action of the English (Morson's) and of the crystallised French preparation (Duquesnel's and Hottot's) with that of the German aconitine. This circumstance alone would appear to indicate, that aconitine is not adapted for hypodermic use, even if the otherwise very doubtful therapeutic properties of the drug recommended it. A watery solution of the drug with the addition of hydrochloric acid (or chloride of aconitine) in a dose of 0·002 to 0·004 gramme ($\frac{1}{30}$ to $\frac{1}{15}$ grain) of the German, or 0·0005 to 0·001 gramme ($\frac{1}{120}$ to $\frac{1}{60}$ grain) of the French preparation may be given.

Curara; Curarine.

Curara has been used for injection in aqueous (acidified with hydrochloric acid), alcoholic, or glycerine solution; the glycerine

[1] *Bull. gén. de thérapeutique*, 1877.

solution is the best (1 to 60), as it can be kept for a longer time unchanged. Gelatine discs, containing 0·0003 gramme ($\frac{1}{200}$ grain), are also suitable. The preparations sold as curara are, as is well known, very unequal in the quantity of the curarine that they contain and in their effects; the dose therefore varies considerably. We may look upon 0·01 to 0·02 gramme ($\frac{1}{6}$ to $\frac{1}{3}$ grain) as about the medium dose; while 0·6 gramme and more than that has been injected without injury, 0·005 gramme has caused the appearance of symptoms of severe shock. *Curarine* and its salts (*sulphate*) in watery solution, as represented by Preyer, may be used in doses of about 0·001 to 0·005 gramme, or $\frac{1}{60}$ to $\frac{1}{12}$ grain (Beigel gave in epilepsy doses of 0·013 gramme); it is dear and, at present, a very uncertain preparation.[1] [The uncertainty attached to the strength of curara is so great that it is always advisable to previously test the activity of a fresh preparation before beginning its use. Of a good preparation 0·0001 gramme will paralyse a frog, and 0·001 gramme a rabbit. 0·005 gramme would form a safe subcutaneous dose of such a preparation in man.—TRANSL.]

Oleandrine.

A non-crystalline, and probably impure alkaloid, obtained from the *nerium oleander*; it has been injected by Erlenmeyer, sen., in epilepsy; in aqueous alcoholic solution, about 0·0001 gramme ($\frac{1}{600}$ grain) and over was used. [According to a recent investigation by Schmiedeberg, the oleander contains, as its active principles, three glucosides, all of which have an action similar to that of digitalin, and one of which, neriin, seems to be identical with digitalin.—TRANSL.]

Coniine.

Soluble with difficulty, and it may be looked on as unnecessary for hypodermic use; it may be given in doses of 0·001 to 0·002 gramme ($\frac{1}{60}$ to $\frac{1}{30}$ grain) in aqueous and alcoholic solution (sometimes even in larger doses without visible injury). [The hydrobromate, a well-crystallised salt, is greatly preferable to the alkaloid itself.—TRANSL.]

[1] Th. Sachs's 'curarine' on analysis consisted merely of phosphate and carbonate of lime, with traces of curara.

Nicotine.

For hypodermic and indeed also for internal use quite valueless. Injected in watery solution in a dose of 0·001 gramme or $\frac{1}{60}$ grain (Erlenmeyer, sen., in tetanus).

Veratrine.

Soluble with difficulty, and locally irritating, and therefore not adapted for subcutaneous administration. Used in alcoholic watery solution in doses of 0·001 to 0·002 gramme ($\frac{1}{60}$ to $\frac{1}{30}$ grain). [Its more soluble salts—hydrochlorate, sulphate, &c. —are now obtainable.—TRANSL.]

Colchicine.

A most impure and unequal preparation, and to some extent locally irritating, and therefore not to be recommended. It has been recently used by Badia, of Barcelona—who appears to have obtained a more soluble preparation—in chronic rheumatism, &c., in doses of 0·002 gramme ($\frac{1}{30}$ grain).

Emetine.

As an emetic, injected subcutaneously, dissolved in water with the addition of sulphuric or hydrochloric acid, in doses of 0·001 to 0·0045 gramme ($\frac{1}{60}$ to $\frac{1}{12}$ grain) for adults; and as an expectorant in less quantity. It is an unreliable remedy, and the resultant physiological action can be better produced by apomorphine, which is much more constant in its action and causes no local irritation.

Quinine; Quinoidine.

The number of preparations of quinine that have been proposed for subcutaneous injection is very large, but we may say that the hypodermic use of this drug has, up to the present, at any rate in Germany, made very little progress, and it is not much in favour. The cause of this lies essentially in the difficulty which we encounter in preparing solutions of quinine

which are good, sufficiently strong, locally non-irritating, which can be preserved, and which are of uniform concentration and action. To attain all this, very many proposals have been made, which we shall do well to discuss as we consider each preparation of the drug.

Pure quinine is, like pure morphine, not adapted for injection, on account of its difficulty of solution. Otto, however, recommended the solution of pure quinine, Bernatzik pure amorphous quinine (purified quinoidine) in ether, as yielding a sufficiently concentrated solution; Otto dissolved 0·5 gramme in 1 c.cm. of ether. This solution, as well as the officinal tinct. chinioidini (Ph. G.), as far as any trials of them go, are rather strongly irritating locally, and are therefore to be rejected as preparations for obtaining the general action of quinine.

Sulphate of quinine (neutral) is soluble with difficulty in water and alcohol, and therefore if we use these menstrua it is not easy to get it or to keep it in the requisite concentration. By the addition of various acids—e.g. sulphuric, whereby the bisulphate is partly produced, hydrochloric (Bernatzik), nitric (Desvignes), tartaric (Bourdon)—chemists have endeavoured to make a preparation which is more soluble and can be kept longer. I have, however, not convinced myself of the benefit of all these proposals, since the acidified concentrated solutions all possess, more or less, local irritating properties, and also are soon decomposed with the partial separation of the quinine salt. Such a solution of the sulphate of quinine which has become turbid by separation of crystals is necessarily quite unsuitable for hypodermic use, not only on account of the uncertain quantity of the drug administered, but also because of the liability to disagreeable local sequelæ—ulceration, abscess, &c. The use of very dilute aqueous solutions certainly does away with these disadvantages; but, if we use these, a fairly large quantity of fluid must be injected at one time, which as a rule is not desirable. Also aqueous solutions of sulphate of quinine, just as those of morphine, soon allow fungi to grow in them. Glycerine solutions, therefore, are better, since the sulphate of quinine is soluble in six parts of glycerine; but it is still better to use the following salt.

Bisulphate of quinine is much more soluble than the pre-

ceding, and therefore more to be recommended for injection. On account of the greater stability of glycerine solutions they are to be preferred to aqueous ones. The bisulphate is soluble on heating in three parts of glycerine, and the clear yellowish fluid remains quite unchanged for months, as I have myself seen. I use a solution of 1 in 10, prepared in the same proportion therefore as the glycerine solution of morphine, to which we may add an equal quantity of distilled water. Without this addition each syringeful, therefore, contains about 0·1 gramme (1½ grain) of the salt; and 1 to 2 syringefuls are, as a rule, sufficient. I have as yet not tried stronger solutions, though probably we could use these without injury.

Hydrochlorate of quinine.—This salt is richer in quinine than the sulphate (83·6 : 74·3), more soluble, more easily absorbed [less apt, if pure, to cause local irritation.—TRANSL.], and less liable to decompose, also, however, half as dear again. It has been used by Bernatzik, Steinhaus, and others for injection, partly in watery solution with the addition of hydrochloric acid, partly also in glycerine solution, 1 to 6. Hydrochlorate of quinoidine is cheaper, and from its solubility and power of absorption especially adapted for subcutaneous injection, particularly the amorphous hydrochlorate of quinine introduced by Kerner, a yellow powder which is soluble in an equal part of water, and which, therefore, permits of great concentration of the solution for injection.

Hydrobromate of quinine, examined by Latour and Boille, and recently recommended by Gubler and Soulez in order to produce the sedative action of bromine, together with that of quinine.[1]—The neutral crystalline preparation, which is richer in alkaloid than the sulphate, is soluble on heating in about 15 parts of water or 4 parts of glycerine. Soulez has used a solution of 1 gramme in 2·5 c.cm. of alcohol and 7·5 c.cm. of water, which I do not consider suitable, as I do not like spirituous solutions. A solution in glycerine made so that a syringeful contains 0·1 gramme (1½ grain) of the salt is better (M. Rosenthal). Such a solution, as I have convinced myself by experiments on animals, is not locally irritating; whether,

[1] See Arduin, *De quelques nouveaux médicaments antipyrétiques.* Thèse de Paris, 1876.

however, this salt possesses any therapeutic advantages over other salts of quinine is doubtful. Soulez used it in extremely large doses (0·4 gramme, or 6 grains, and, in attacks of intermittent fever, even 0·6 to 1 gramme) subcutaneously.

Citrate of iron and quinine.—M. Rosenthal's recommendation of this compound deserves great respect, especially in those cases in which the combined use of quinine and iron is indicated. The amount of quinine contained in it is indeed somewhat small, also this salt is not so soluble as other salts of quinine. We get a brownish green liquid of the consistence of oil when we dissolve it with heat in about ten parts of glycerine, which, when diluted with water, may be used for injection. Berg, of Dresden, recommends a 'green citrate of iron and quinine,' as prepared according to Von Walter's prescription ; it is said to be much more soluble and stable than the preparation of the German pharmacopœia, the amount of quinine in which as compared with that in the former is as 4 to 5.

The recommendations by different physicians of other salts of quinine, such as the bitartrate, bilactate, valerianate, formate, quinate, &c., are scarcely worthy of mention. On the other hand, we may notice combined injections of quinine and morphine, which were proposed especially during the cholera epidemic of 1866 and 1867, and lately also by Lubanski and others. Lubanski combines 1 c.cm. of a 1 to 20 aqueous solution of the hydrochlorate of morphine with 1 to 2 c.cm. of a 1 to 10 aqueous solution of quinine. Here, however, glycerine solutions would be advantageous.

Pilocarpine.

The alkaloid of jaborandi, as prepared by Merck, has rightly gained for itself universal recognition in the past two years, and is employed with especial advantage in the form of subcutaneous injection. For this purpose we use almost exclusively a 2 per cent. solution of crystalline hydrochlorate of pilocarpine. 1 c.cm. (15 mins.) of this solution appears to be equal to 5 c.cm. of the infusion of jaborandi in activity and in the amount of the alkaloid contained in it. This is the full dose, which only rarely is to be exceeded ; in some cases, 2

syringefuls of the above solution may be given = 0·04 gramme ($\frac{3}{5}$ grain) of pilocarpine. Therapeutically it has been used extensively, and recommended especially to excite tissue metamorphosis, and as a diaphoretic and sialogogue, &c., in syphilis (Lewin, Lockwood); recently also in colic from lead poisoning (Bardenheuer), eclampsia and uræmia (Fehling, Boegehold, Von Stroynowski, Bidder, Prochownich); as well as a means of exciting labour pains in pregnant and parturient women (Maassmann, Felsenreich, Kleinwaechter, P. Müller, Parisi, Saenger, Schantz, Welponer, and others). [Pilocarpine is apt to be mixed with more or less of jaborine, an alkaloid, which, according to Harnack and Meyer, is a decomposition product of pilocarpine, and is very similar in action to atropine. It is sometimes present in so large quantity that the peculiar action of the pilocarpine is altogether lost.—TRANSL.]

Preparations of Ergotine.

These preparations lay claim to special interest for the practice of hypodermic injection. Their therapeutic use, especially in hæmorrhages of very different organs, such as in chronic uterine affections (metritis chronica and fibro-myomata), in diseases of the vessels (aneurisms, varices), goitre, vasomotor neuroses, congestion of the brain, &c., is tolerably widespread, and would without doubt be much more so if we were in possession of a solution for injection which satisfied all our demands and was not disagreeable to use on account of the pain and local irritation which it causes. Many different and more or less happy attempts have been made to obtain such a solution, but a decisive result can only be expected when we have succeeded in isolating the active constituent of the secale cornutum with absolute certainty and in obtaining it as a chemically pure crystalline body. The supposed alkaloids, the ergotine and ecboline of Wenzell, the ergotinine of Tanret, &c., have, as we well know, shown themselves to be impure compounds; sclerotinic acid, discovered by Dragendorff, appears to possess the action of the drug, but is not the only principle which does, since scleromucin is also believed to be active; but even these have not as yet been obtained perfectly pure.

The officinal *extractum secalis cornuti* of the German pharmacopœia—as a rule badly named ergotine—is, as is well known, an aqueous extract (Bonjean's ergotine). Physicians have used this in aqueous, alcoholic, or glycerine solutions; the last-named are best in the proportion of 1 to 3, to which an equal quantity of water is added; thus ext. secalis cornuti 2·5, glycerini et aq. dest. ana 7·5; 1 to 2 syringefuls of this (or about 0·15 to 0·3 gramme, or $2\frac{1}{4}$ to $4\frac{1}{2}$ grains of the extract), may be used for one injection. The injection of this solution, however, is always somewhat painful, and is often accompanied by the formation of small obstinate lumps or indurations at the seat of puncture. This is even more true of the alcoholic or pure aqueous solutions, the latter of which are also liable to rapid decomposition from the presence of fungi, which set up fermentation. In order to prevent or to restrict as much as possible these evils, preparations are now made which have been purified by repeated extraction or by dialysis, such as the so called *ergotinum bis purificatum* (Wernich's ergotine). This is first extracted with ether and then with absolute alcohol, the residue digested with water and placed in the dialyser for three days. The activity of this preparation has been proved by numerous trials, and there are no theoretic objections to it, since sclerotinic acid and scleromucin, which are probably the principal active constituents of the substance, are contained in the extract so prepared; still the local irritant action is in general not much less, and the stability of the solutions is not very great. The latter can be much increased, according to Winkel, by the addition of a very small quantity of salicylic acid, or, according to our experiments, still better by carbolic acid. Berg,[1] of Dresden, recommends a freshly dialysed extract (*ergotinum dialysatum*). Another preparation expressly intended for injection, the mode of making which is as yet a secret, is that recommended by the druggist Bombelon, of Neuenahr,—'*ergotinum liquidum pro injectione.*' It is relatively dear (a bottle containing 25 grammes, or about 7 drachms, costs, if obtained direct from the maker, 6*s.*), but appears to be useful for hypodermic use, from its greater stability, pain-

[1] Gesellschaft für Naturwissenschaft und Heilkunde in Dresden. Vide *Deutsche Zeitschrift für prakt. Med.*, 1878, No. 45.

lessness, and from the fact that it is not followed by disagreeable local symptoms; whether it is quite equal in activity to the usual extract must be determined by further experience. At my suggestion Bombelon's preparation has been repeatedly used by Professor Pernice in his gynæcological clinic, and he expresses himself as on the whole satisfied with it. Besides this, Savory's gelatine discs, each of which is said to be equal to 0·02 gramme ($\frac{1}{3}$ grain) of ergotine, are also used.

I have lately often used *sclerotinic acid* for injections (prepared by Witte, of Rostock, according to Dragendorff's method). This substance is a yellowish brown powder, soluble in water and diluted alcohol, which exists in ergot of rye to the extent of 3 to 5 per cent.; the usual dose is accordingly about 0·03 to 0·05 gramme ($\frac{1}{2}$ to 1 grain). The injections are somewhat painful, but I have not seen signs of violent local irritation after its administration. The use of the salts of this acid is, perhaps, still more suitable, amongst which *sclerotinate of lime* and of *soda*, the latter of which has been lately investigated by Nikitin,[1] are well adapted for administration. [From a very recent and extended investigation by Kobert, it appears that *ergotinic acid*, which is the main constituent of sclerotinic acid, has no action on the uterus; and Tanret's ergotinine is equally without action. The really active principles of ergot seem to be *sphacelic acid*, which produces powerful contraction of the arteries, and *cornutine*, which causes contraction of the uterus. But none of these are as yet to be purchased. Kobert states that there exists as yet no preparation of ergot suitable for subcutaneous injection.—Transl.]

Gelsemium; Gelsemine, Gelseminine.

I have made several trials on men and animals of the subcutaneous application of the *tincture* or the *aqueous extract* of *gelsemium*, as well as of '*gelsemine*,' a yellow amorphous powder soluble with some difficulty in water (1 in 116), as prepared by Prommsdorf, and these trials have shown me that

[1] Rossbach, *Pharmakologische Untersuchungen*, iii. parts i. and ii. Würzburg, 1879.

the remedy is not altogether ill adapted for this method. The dose of the tincture is 0·5 c.cm. (8 mins.), of gelsemine 0·01 gramme ($\frac{1}{6}$ grain); this, however, may without doubt be exceeded. Savory's gelatine discs are said to correspond to 10 minims of the tincture. *Hydrochlorate of gelseminine*, which was introduced by Sonnenschein, has shown itself, after recent trials of it which I have made, to be still more worthy of recommendation for hypodermic use, in an aqueous solution of 1 to 200. It is ten times as strong as gelsemine, and therefore the dose is about 0·001 gramme.

Digitalin.

We have here, as already mentioned, to do with the difficulty, that very different preparations in kind and activity are sent out of the laboratories and are sold as 'digitalin.' Only *Nativelle's digitalin* (at present not to be got) is a crystalline preparation; other kinds, as, e.g., *Merck's amorphous digitalin*, which is most used in Germany, are, it appears, more or less mixed with digitalein, digitoxin, &c. As a result of this, the statements as to its action are very varying and to some extent contradictory, as, e.g., Otto, in opposition to the usual recommendation of it as an antipyretic, says that he has observed a rise of temperature ('digitalin fever') after an injection of Merck's preparation of the drug in epileptics who were free from fever. Otto's statements are, however, disputed by Witkowski and Gerber; and I, for my part, have never seen such results follow the use of this preparation. Dose, 0·001 to 0·003 gramme ($\frac{1}{60}$ to $\frac{1}{20}$ grain), and upwards, in aqueous or better in glycerine solution; of Nativelle's digitalin, about 0·001 gramme, according to Adrian, in a weak alcoholic solution. Gelatine discs contain 0·006 gramme ($\frac{1}{100}$ grain).

[Many active principles, derived from other plants than digitalis, have in recent years been found to possess an action apparently identical with that of digitalin. Of these, *helleboreïn*, *antiarin*, *strophanthin*, and *erythrophleine* are especially worthy of trial for subcutaneous injection, since they are more soluble than digitalin.—TRANSL.]

Saponine.

This, as far as my experiments with it on man and animals go, is not fitted for subcutaneous injection, as the solutions usually set up local irritation, obstinate indurations, &c. An aqueous solution of 1 to 50 is used. The dose of saponine is 0·01 to 0·06 gramme ($\frac{1}{6}$ to 1 grain).

Cannabis.

Tincture of cannabis indica has been repeatedly injected instead of morphine as a narcotic, but it is somewhat superfluous. The dose is 0·25 to 0·5 gramme (4 to 8 grains).

[*Cocaine.*

Very recently the active principle of *erythroxylon coca* has been used as a local anæsthetic. Although mainly applied epidermically, it is sometimes injected subcutaneously, for the relief of pain, in the form of a 1 to 5 per cent. solution of the hydrochlorate, the dose being 5 to 20 minims.—Transl.]

Tayuya.

This, which has lately been much recommended as an antisyphilitic and antistrumous remedy in Italy, and which is the root of *dermophylla pendulina*, has been proposed for injection, and in the form of the undiluted tincture in a dose of 1 c.cm. (15 mins.) Experiments which I made with the tincture got from Ubicini, of Padua, did not show any considerable activity when used in the above dose.

Kamala.

Luton proposes to inject into hydatid cysts tincture of kamala, as practised in India. Macerate 180 grammes of kamala with 380 grammes of alcohol; the dose per 24 hours for internal administration is 4 to 16 c.cm. (1 drachm to $\frac{1}{2}$ ounce).

Oil of Turpentine.

Used by Luton in an obstinate case of sciatica. The injection of 1 gramme (15 mins.) of pure oil of turpentine produced the formation of a somewhat large abscess.

Camphor.

I was the first to use injections of this substance in great adynamia and collapse in acute diseases; it has also been used extensively as a palliative remedy in cholera, typhus fever, &c. We may administer solutions of the drug in ether, or in alcohol (spiritus camphoræ), or in oil (oleum camphoratum); [1] symptoms of local irritation are, especially when we use the last preparation, not so intense as we should perhaps expect, and as a rule the pain, even if the patient be much prostrated, is not very acute. Dose 0·1 to 0·2 gramme ($1\frac{1}{2}$ to 3 grains) = 1 to 2 c.cm. of the oleum.

Musk.

This has been much used, just as camphor is, as an analeptic in the algide stage of cholera, in typhus fever, &c. Aqueous solutions (Rohde), or better still the *tinctura moschi*, which is officinal in the German pharmacopœia,[2] may be administered, the latter preparation in a dose of 1 c.cm. (15 mins.) or more.

Cinnamon.

Tinct. cinnamomi was once injected by Luton in the neighbourhood of a carcinomatous growth in a dose of 5 c.cm. (75 mins.); the local irritation was not very great.

Cantharides.

Tinct. cantharidis was injected by Ruppaner in a case of sciatica in a dose of 25 drops; violent pain followed its use, and four days afterwards an abscess formed. Luton, however, only found redness and a slight induration, with no further effects, after the injection of 20 drops.

[1] [Ph. Germ.—10 per cent. solution in olive oil.—TRANSL.]

[2] [1 part of musk digested in 25 parts of rectified spirit and 25 parts of water.—TRANSL.]

Croton Oil.

Suggested for the production of local inflammation and the formation of an abscess.

Aloes.

This substance was injected in aqueous solution (1 to 10) by Luton, who used 1 c.cm. (15 mins.) of the solution, and it is said to have caused only very slight local irritation (hyperæmia), and to have been followed by active purgation. It is just possible that *aloin* may be of service in subcutaneous injection in suitable cases. [It is very doubtful whether aloes or aloin exerts a purgative effect when injected subcutaneously.—Transl.]

Elaterium

Has been used subcutaneously in England. Gelatine discs contain 0·005 gramme.

Organic Acids (Hydrocyanic, Benzoic, Carbolic, Lactic, Acetic, and Tannic).

Hydrocyanic acid has been used in dilute solution by McLeod in cases of insanity. Luton used *cyanide of potassium*, but the injection of a 1 per cent. solution of it is very painful and produces symptoms of inflammation. *Aqua lauro-cerasi* was injected by Estachy[1] in a dose of 2 c.cm. (30 mins.), in lumbago, and Luton recommended its administration as a menstruum for injection solutions, especially those of morphine, in order to protect them against decomposition from the growth of fungi. But we cannot look upon the hydrocyanic acid contained in this preparation as quite inactive when large quantities are given.

Benzoic acid has been used as a stimulant and analeptic in the same cases as camphor and musk, either alone or in combination with the former (Rohde). An alcoholic solution of it, 1 to 12, may be used, of which 1 to 2 syringefuls may be

[1] *Bull. gén. de thér.*, March 15, 1878, p. 223.

given at one time; or 1 gramme (15 grains) of camphor and 1·5 gramme (22 grains) of benzoic acid may be dissolved in 12 c.cm. ($\frac{1}{2}$ ounce) of alcohol, and some of it injected, but this is very painful.

Acetic acid is only used for parenchymatous injections, especially to destroy carcinomatous growths (first proposed by Broadbent and Randall in 1867). It is important to remember that the injection of dilute acetic acid, or of the so called Villate's solution, which contains free acid, may be dangerous, from the deleterious action of the acid on the circulating blood if it come into direct contact with it. Sudden death has been repeatedly observed after its use. Lately Mackenzie has recommended the injection of dilute acetic acid, 1 to 11 of water, of which 5 to 20 drops may be injected in chronic indolent swelling of the lymphatic glands of the neck, in order to disperse them.

Carbolic acid has recently been extensively injected as a local antiphlogistic in inflammations of the skin, of the subcutaneous tissue, of the lymphatic glands, joints, larynx and throat, &c., as well as a local antineuralgic remedy; also for the destruction of tumours, osteochondromata (Hüter), nævi (Bradley), splenic tumour (Mosler), &c. A two per cent. aqueous solution has almost exclusively been used, of which 1 to 2 syringefuls is the dose for injection, = 0·02 to 0·04 gramme ($\frac{1}{3}$ to $\frac{2}{3}$ grain) carbolic acid; larger quantities may be given by means of Hüter's infuser. The subcutaneous use of such a solution is almost painless, and produces no symptoms of local irritation; on the other hand I found that parenchymatous injections into strumous cervical glands were very painful.

Lactic acid has been used by Hüter and Vogt for parenchymatous injection in osteochondromata. *Lactate of soda* was subcutaneously administered by L. Meyer as a 'depressing remedy' (according to Preyer) in a dose of 0·6 gramme (10 grains); it had, however, no hypnotic action, but was accompanied by great pain at the seat of puncture.

Tannic acid (*tannin*) was injected by Luton in order to act as a derivative by the production of local fluxion or congestion; solution of 1 to 10 or 1 to 5, of which 1 to 2 c.cm. (15 to 30 mins.) is the dose. Schwalbe injected 1 to 4 per cent.

solutions of tannin in carcinomata, and also at the painful spots in neuralgia of the fifth nerve (vide infra, as to the administration of iodine and tannin).

Alcohols and their Derivatives (Alcohol, Ether, Spiritus Ætheris, Acetic Ether, Chloroform, Iodoform, Hydrate of Chloral, Nitrite of Amyl).

Alcohol is employed partly as a solvent of active remedies, partly, by itself, as a means of producing symptoms of local irritation ('congestion douloureuse' or 'substitution de douleur,' according to Luton), also for parenchymatous injection in lipomata (Haase), carcinomata, strumous glands (Schwalbe), &c. Luton used a solution containing 90 per cent. of alcohol and often injected 5 c.cm. (75 mins.) of it at once. *Ether* has also been used partly as a solvent, partly for its own action as a stimulant and restorative in threatening collapse in acute diseases, in shock after operations, labour, profuse losses of blood, &c. Injections of 1 c.cm. (15 mins.) or more of ether are somewhat painful, but do not appear as a rule to produce any severe local reaction. *Spiritus ætheris* (Zülzer) and *acetic ether* (Bumüller) may be similarly used as analeptics.

Chloroform, especially in England and America, has often been injected in cases of neuralgia in doses of 2 c.cm. (30 mins.) The effect is, however, very questionable, and violent local symptoms are easily induced, so that I do not consider the practice to be judicious. Recently Collins[1] has injected a mixture of chloroform with atropine and morphine, as well as chloroform alone, in three cases of sciatica, with good results.

Hydrate of chloral is not well fitted for subcutaneous use, since, in order to administer effective doses, relatively large quantities of fluid must be injected, and the injections as a rule are very painful, and often produce signs of local irritation or cauterisation, erythema urticaria, cutaneous or deeper ulcerations, abscesses, sloughing, &c. This is especially the case with concentrated solutions (1 or 2 parts of chloral hydrate to 1 part of water), such as Urtel[2] has recently recommended in

[1] The *Clinic*, Nov. 22, 1874.
[2] *Allg. Zeitschrift für Psychiatrie*, vol. xxxv. 1878, part ii. p. 206.

the case of lunatics; the dose of the drug is 0·5 to 3 grammes (10 to 50 grains), average 1·25 gramme (20 grains). The combination of chloral hydrate with morphine, which Vidal[1] and Estachy among others have lately recommended for subcutaneous injection—

℞ Chloral hydrat. . .	0·5 gramme	(8 grains)
Morph. hydrochlor. . .	0·25 ,,	(4 grains)
Aq. dest.	25·0 c.cm.	(1 ounce)

—cannot present any material advantage. The addition of a small amount of hydrate of chloral to solutions of morphine does, as already mentioned, appear to prevent the growth of mycelium in them.

Iodoform does not appear to have as yet been subcutaneously administered to human beings. According to the experiments on animals of Binz and Högyes,[2] small quantities of it do not usually excite any local changes, while large doses of it are capable of producing coagulation in the connective tissue meshwork, and abscess.

Amyl nitrite may be administered subcutaneously; but, as in the case of chloroform, the inhalation of the drug is to be preferred.

Carbohydrates, Glycerides, Albuminoids, and other Food Stuffs.

Menzel and Perco injected a solution of *sugar* into dogs; Krueg[3] did this along with other foods in the case of an insane person who refused to take nourishment.

Diastase, in aqueous solution, 0·1 to 0·2 gramme ($1\frac{1}{2}$ to 3 grains), was administered by Kussmaul, with no good effect.

Fats (in fluid form) were injected by Menzel and Perco into dogs, and were absorbed after 48 hours without any bad symptoms; *milk* and the *yolk of egg* were given with the same result. Krueg injected *olive oil* in the case of the patient alluded to, in quantities of 15 to 30 grammes ($\frac{1}{2}$ to 1 ounce),

[1] *Trib. méd.* 1875, p. 364.

[2] *Archiv für experimentelle Pathologie und Pharmakologie*, viii. 1878, p. 309; x. 1879, p. 228.

[3] *Wiener med. Wochenschrift*, 1875, p. 34.

daily by means of a syringe holding 15 grammes, and when injected slowly the operation was painless and only produced a little redness. He also injected the whole of the yolk of an egg, beaten up and strained, which produced a low form of inflammation and suppuration, with bursting of the abscess after some months. Whittaker injected with success *milk* and *meat juice* alternately, to the extent of 4 c.cm. (60 mins.) every 2 hours, in a case of gastric ulcer. Mosler made some experiments with *cod-liver oil*, with which, however, symptoms of local irritation were several times produced.[1]

Glycerine is used as an excellent solvent for various alkaloids (morphine, curara, quinine), as also for ergotine, digitalin, iodine, &c. The glycerine employed for this purpose must be chemically pure, as otherwise it may have an irritant action. Whether the results obtained by experiment by Luchsinger, who produced hæmoglobinuria after the injection of this substance under the skin of rabbits, and also under certain circumstances in man, deserve much regard may for the time be left unsettled.

Blood.—Subcutaneous injection of defibrinated blood has been very lately carried out by different physicians, in the hope that this proceeding might be a substitute for transfusion. This hope is, according to experiments made by Ehrlich [2] at my suggestion, quite illusory, inasmuch as the morphological elements of the foreign blood are broken up and form detritus at the place where it is injected, and none of it is transferred to the blood of the animal operated on. Also the hæmatin is probably either not at all or only to a very small extent absorbed. Cazeneuve [3] was not able to detect any increase of the urinary pigments or the appearance of bile pigments after the subcutaneous injection of blood or of a solution of hæmatin. There remains, therefore, only the serum as the substance which is

[1] Vide also the published experiments of Pick ('Ueber Ernährung mittelst subcutaner Injectionen,' *Deutsche med. Wochenschrift*, 1879, No. 3, p. 31). Almond oil, cod-liver oil, milk, yolk of egg, and defibrinated blood were used as nutritious fluids for injection, in doses of 1 to 6 grammes (15 to 100 mins.) Inflammatory reddening often ensued at the seat of puncture.

[2] *Einspritzungen von Blut ins Unterhautzellgewebe.* Dissertation. Greifswald, 1875.

[3] Proceedings of the *Soc. de biologie* of May 19, 1877.

capable of absorption, and, under certain circumstances, of acting as a nutriment. As a matter of fact blood serum, especially that of horses, has been subcutaneously administered by Hüter with the infuser in anæmia and cachexia due to profuse suppuration or to large losses of blood. Caution, however, is necessary in carrying out such an operation, at any rate in so far as we use injections of the blood of animals in man, inasmuch as the serum of a different species of animal acts as a solvent of human blood corpuscles, as the numerous experiments on the infusion of serum made by Landois[1] prove. Horses' serum, as also that of lambs, appear to have only a very slight solvent action on human blood at the usual temperature of a room; still at the temperature of the body this action may progress more quickly.[2]

Pepsin in aqueous solution has been much used for parenchymatous and interstitial injections into tumours, especially carcinomata (Thiersch, Nussbaum), also into chronic swellings of the lymphatic glands (Mackenzie); but on the whole it is not so useful for this purpose as other remedies, especially nitrate of silver.

INORGANIC REMEDIES.

Water.

Injections of ordinary or distilled water have been prescribed by many physicians as a sedative in painful affections, neuralgia, &c. (Potain, Lafitte, Lelut, Lucas, Dieulafoy, and others). Accurate control experiments, such as Dujardin-Beaumetz made, show the absolute untenability of this view. Beigel injected subcutaneously large quantities (as much as 7 ounces) of water in the stage of asphyxia of cholera by means of an indiarubber bag, the compression of which drove the fluid into eight cannulæ at one time; for this purpose, however, the infuser would be more suitable.

[1] *Die Transfusion des Blutes*, Leipzig, 1875, pp. 149–183.

[2] Also the more recent experiments of Casse with the subcutaneous injection of defibrinated blood in man and animals yielded negative results.

Iodine (*Tincture, Oil, Glycerine, Tannate, &c.*)

Iodine has been used dissolved in different media (aqueous solution of iodide of potassium, spirits of wine, oil, glycerine, and aqueous solution of tannic acid) for hypodermic, still more for submucous, parenchymatous, and interstitial injection, in swelling of lymphatic glands, enlarged tonsils, goitre, cystic tumours of very various kinds, spina bifida, enlarged bursæ and nævi. Tincture of iodine, either undiluted or diluted with water, is used; or a solution of iodine in iodide of potassium in the proportions of the well-known Lugol's solution; or glycerine of iodine 1–2 to 100; or oil of iodine 1 to 10 (Luton). For the preparation of a solution of iodine and tannin, in which the iodine appears to be chemically combined, since no reaction with starch is produced with it, Guilliermond gives the following recipe: 1 part iodine and 2 parts tannin dissolved in 18 parts aq. dest., and reduced to 10 parts by evaporation; this is especially recommended as a hæmostatic in varices, &c. Iodic acid, iodide of potassium, and of sodium, &c., are sometimes employed.

Bromine.

Used as an injection in the vicinity of wounds in cases of hospital gangrene, together with its simultaneous use as a dressing (Goldsmith). Bromide of potassium, &c.

Bisulphide of Carbon.

Used, but without success, as a stimulating injection in the asphyxiated stage of cholera (Von Gräfe).

Inorganic Acids (*Sulphuric, Nitric, Hydrochloric, Iodic*).

Sulphuric acid appears to have only been used in experiments on animals (Nélaton and Anger); nitric acid, on the other hand, also in man, as an injection in carcinomatous growths (Bennet); also hydrochloric acid (Heine; Mackenzie tried it in swellings of the cervical glands). Iodic acid was recommended by Luton, in aqueous solutions 1 to 5 and 1 to

10, as a resolvent and caustic in carcinomatous tumours, ganglia, &c., 1 to 2 c.cm. (15 to 30 mins.) of the above solution being the dose. It is about equal in painfulness to tincture of iodine.

Iodides of Potassium and Sodium.

These are used for subcutaneous and parenchymatous injection in scrofulous and syphilitic glandular swellings, periosteal nodes, strumous swellings, &c. From the rapid absorption, to which we have before alluded, a considerable local action of the iodine cannot be expected from these salts. Concentrated solutions of iodide of potassium, 1 to 3, may, as I myself and also Luton have observed, produce intense tissue irritation and even suppuration.

Bromide of Potassium.

The substitution of the subcutaneous application for the internal administration of this remedy does not appear advantageous, on account of the large quantity of fluid that must in general be injected. Concentrated solutions of it, 1 to 3, are locally irritating, but to a less extent than iodide of potassium.

Chloride of Sodium, Chloride of Magnesium, Sulphate of Magnesia.

Chloride of sodium has been used for the most part as a counter-irritant, to produce 'substitution parenchymateuse' (Luton) in painful affections of very various kinds, neuralgia (especially sciatica), lumbago, pleuritic pains, &c. According to the concentration of the fluid used (Luton employed cold saturated aqueous-alcoholic solutions of sea salt), we can produce simply painful irritation or suppuration; as Luton remarks, the prospects of the appearance of suppuration increase as the place of injection is further removed from the centres and from the trunk. If the solution be well filtered the probability of it is less. Also it has been proposed to inject salt in order to make the blood of better quality (in cholera), as also to increase

the digestive power. Lubanski says that he has observed increase of the appetite, and also a favourable influence on the diarrhœa of phthisis, after its use.

Chloride of magnesium is said not to be locally irritating, but to possess a laxative action on being subcutaneously injected (Luton). The same is true of sulphate of magnesia. [The Translator has lately proved that this is not the case. Saline purgatives do not act when injected subcutaneously; or, if they do, it is only when they are injected over the abdomen, and in virtue of a reflex effect.]

Liquor Potassæ, Carbonate of Potash. Ammonia, Anisated Ammonia, Carbonate of Ammonia, Sulphide of Ammonium, &c.

Liquor potassæ is only used in animals in order to produce sloughing (Nélaton and Anger). Luton thinks that solutions of carbonate of potash may be useful as injections in man, in order to get rid of tumours containing sebaceous material, such as wens, steatoma, &c., by saponification and solution.

Liq. ammoniæ[1] diluted with 2 parts of water has been employed as an irritating injection in pseudarthrosis, between the two ends of the broken bone (Bourguet); 6 to 7 drops of the solution are sufficient. Halfort injected very dilute solutions of ammonia in snake-bite and collapse.

Liq. ammoniæ anisatus[2] has been subcutaneously applied by Zülzer as well as myself as a stimulant and analeptic, either alone or diluted with 1 or 2 parts of water, 5 to 7 drops being used for one injection. *Sulphide of ammonium* has been injected by M. Hirsch (Mainz) in cholera.

Carbonate of ammonia appears to have been injected only in animals (Liouville and Béhier); 2 grammes are said to have caused epileptiform attacks and fall of temperature in guinea-pigs and rabbits.

[1] [The German liquor ammoniæ is about the same strength as the English. —TRANSL.]

[2] [Liquor ammoniæ anisatus of the German pharmacopœia contains

1 part of ol. anisi,
5 parts of liq. ammoniæ,
24 „ rectified spirit. TRANSL.]

Solution of Chlorinated Soda.

This fluid, containing hypochlorous acid ('liqueur de Labarraque'), has been injected into the skin of the eyelids by Gentilhomme,[1] of Rheims, once in a case of carbuncular œdema of them. He used a solution of 1 to 10, and this caused an erysipelatous swelling extending to the scalp. Experiments with the subcutaneous injection of this substance in rabbits poisoned with splenic fever yielded no positive results. Just as little did the experiments which Colin made on the same animals with subcutaneous injection of iodine, ammonia, acetate of ammonia, &c., in cases of splenic fever and septicæmia.

Liquor Arsenicalis (*Fowler's Solution*).

The officinal liq. arsenicalis[2] is diluted with 2 to 3 parts of water, so that each dose amounts to 0·15 to 0·2 c.cm. (2 to 3 mins.) of the liquor. It has been recommended on account of its local effect in malignant tumours, glandular lymphomata, splenic tumour, &c., as well as for the purpose of producing the general action of arsenic in chorea, tremor, and other neuroses, psoriasis, &c.

Tartar Emetic.

Not to be recommended as an emetic on account of its very strong locally irritant action, which sometimes results in suppurating phlegmon, lymphangitis, &c. It has been used for parenchymatous and interstitial injections, in nævi, sebaceous cysts, &c. (in solutions of 1 to 30, Grenell); also in saturated solution in order to set up a higher degree of counter-irritation —'substitution inflammatoire' of Luton—1 c.cm. (15 mins.) of the cold saturated solution.

[1] *Soc. méd. de Reims* (bull. II.), 1872, p. 68; Luton, *Traité des injections sous-coutanées à effet local,* p. 330.

[2] [The German preparation (1 in 100) is very slightly stronger than the English (1 in 110).—Transl.]

Preparations of Iron (Ferrum Dialysatum, Ferrum Peptonatum, Pyrophosphate of Iron with Citrate of Ammonia or with Citrate of Soda, Ferrous Tartrate, Lactate of Iron, Liquor Ferri Perchloridi).

Dialysed iron, a dark brown fluid, has been injected by Da Costa in anæmia in a dose of 15 drops, diluted or not with water. This preparation ought to contain 5 per cent. of oxide of iron; according to M. Rosenthal it is more stable and more suitable for injection if mixed with an equal part of glycerine. *Albuminate of iron*, which has been lately recommended, and which by digestion with a solution of pepsin is changed into *peptonised iron*, is more useful. I found that a preparation of the latter, made by Friedländer of Berlin, containing 2 per cent. of iron, was suitable for subcutaneous injection in animals.

Pyrophosphate of iron with citrate of ammonia was recommended by Huguenin,[1] and recently the same salt of iron with citrate of soda by M. Rosenthal,[2] for subcutaneous injection in anæmia, &c. Of the former, an aqueous solution (1 to 5) was used, so that the syringe contained 0·03 gramme of iron; the latter, containing 26·6 per cent. of iron, in aqueous solution (1 to 6), was employed, of which a half to a whole syringeful is to be given at one time. The solution ought to be freshly prepared, or at most be only a few days old, since it soon becomes turbid from the growth of fungus, especially in summer. The iron can be found in the urine 30 minutes after the injection.

Ferrous tartrate has been used by Rosenthal in aqueous solution in a dose of 0·24 gramme (4 grains) in a syringeful. It appears to have caused symptoms of irritation (redness, swelling, and obstinate induration). The same holds good of *lactate of iron*, according to my experiments with it. (As to citrate of iron and quinine, vide Quinine). Ferrocyanide of potassium is not injected for therapeutic purposes.

[1] *Correspondenzbl. für Schweiz. Aerzte*, 1876, No. 11.
[2] *Wiener med. Presse*, 1878, Nos. 45–49.

Liquor ferri perchloridi has been much employed for parenchymatous and interstitial injections, especially in erectile tumours, carcinomatous growths, &c.; but even a dilute solution of perchloride of iron, on account of its liability to cause embolism, especially in children, is not without danger, as is testified by many fatal cases after the injection of it in nævi.

Sulphate of Copper.

Used as an emetic (Lissauer), also to dissipate buboes (Daniels), or to set up strong local derivative action in the form of suppuration (Luton). The drug is in no way to be recommended; it is not so useful as nitrate of silver as a local irritant, and in addition to this produces symptoms of poisoning much more quickly.

Sulphate and Chloride of Zinc.

Both salts have been proposed for interstitial caustic injection, the chloride especially for carcinomatous tumours (Moore, Reichel, Heine, and others). Luton recommends for this purpose aqueous solutions of 5 or even 10 per cent., in order to set up sloughing with certainty.

Nitrate and Hyposulphite of Silver.

Nitrate of silver has been used especially in order to produce irritative tissue changes, as a counter-irritant in painful affections, neuralgia, &c., also for parenchymatous and interstitial injections in carcinomatous tumours, in enlarged lymphatic glands (Mackenzie), in erectile tumours (Bigelow), &c. Luton looks on this salt as the best of all 'substitutifs parenchymateux,' because as a rule its local action is sharply defined, with central sloughing and peripheral induration, and the suppuration that follows is circumscribed. For this purpose he uses solutions of 1 to 5 or 1 to 10, of which $\frac{1}{4}$ to 1 c.cm. (4 to 15 mins.) is to be injected at one time, and advises the use of crystallised in preference to fused nitrate of silver, in order to make the quantity more accurate. For injection into carcinomatous tumours,

in which we do not wish to bring about the formation of one slough, but an endosmotic penetration into the cells (Thiersch, Nussbaum, Albanese, &c.), very dilute solutions, 1 to 5,000 to 1 to 2,000, are employed; after which a solution of chloride of sodium half as strong again as the solution of the silver salt is injected.

Also in tabes dorsalis the injection of nitrate of silver has been tried (Frommhold); but this cannot be recommended, on the one hand because of the local irritant action, on the other because of the transformation of the silver salt into an insoluble form at the seat of injection. Another preparation of silver, however, appears to be useful as a substitute for the internal administration of silver (whereby a large part of the silver administered becomes inactive from the formation of insoluble compounds), and may be employed subcutaneously in neuroses, viz. *hyposulphite of silver and soda*, which can be obtained by dissolving freshly precipitated chloride of silver in a solution of hyposulphite of soda. Jacobi gives the following formula for its preparation:—

℞ Argenti chloridi	0·05 part
Sodii hyposulphit.	0·30 „
Aq. dest.	10·00 parts

Mix and keep in a dark bottle.

This gives us a $\frac{1}{2}$ per cent. solution, which remains for weeks almost unchanged; if more concentrated, sulphide of silver quickly separates out. It causes, as I can testify from experiments on animals, no caustic or coagulating local action. The dose of it for injection in adults is about 1 c.cm. (15 mins.)

Preparations of Mercury (Calomel, Corrosive Sublimate, Iodide of Mercury, Cyanide of Mercury, Albuminate of Mercury, and Peptonate of Mercury).

Corrosive sublimate is the preparation of mercury that has especially been employed subcutaneously, and usually in aqueous solution, on account of its solubility; 1 c.cm. (15 mins.) of a 1 per cent. solution = 0·01 gramme ($\frac{1}{6}$ grain) of the salt, is an ordinary dose for this purpose. Doses of 0·03 to 0·06 gramme ($\frac{1}{2}$ to 1 grain) may, according to Lewin, cause symptoms of

poisoning. The dilution mentioned does not in general give rise to any violent symptoms of local irritation, merely painful swelling and redness, and rarely suppuration, being produced. Since aqueous solutions, after being long exposed to the light, are apt to be decomposed with partial precipitation of the perchloride of mercury, glycerine may be used instead of water as a solvent (Rosenthal); or Savory and Moore's gelatine discs, each of which contains about 0·004 gramme ($\frac{1}{16}$ grain), are useful. In order to prevent the pain of the injections it has been proposed to administer a combination of corrosive sublimate and morphine. Liégeois's formula is the following:—

℞	Hydrargyri perchloridi	0·2 part
	Morphiæ hydrochloratis	0·1 ,,
	Aq. dest.	90·0 parts

This gives us a very dilute solution, of which about 1 c.cm. (15 mins.)=0·002 gramme ($\frac{1}{30}$ grain) of the mercuric salt, is the dose for injection.

If we wish to produce a local caustic action much stronger solutions must naturally be used: e.g. Bienfait, of Rheims, used in the carbuncles of anthrax (as an injection into the œdematous eyelids) an alcoholic solution of 1 to 5; Luton, some drops of an alcoholic solution of 1 to 30; Dominguez, 20 to 80 drops of a 10 per cent. solution in elephantiasis Græcorum.

More recently many different attempts have been made to modify the solutions of corrosive sublimate employed in syphilis, in such a way that they may be more diffusible and assimilable, and at the same time cause less pain and be more stable. This may be managed either by making a neutral solution of *corrosive sublimate with chloride of sodium* (Stern, Reder and Gschirhakl) or by changing the sublimate into an *albuminate* or *peptonate of mercury*, as Bamberger first proposed.

The first method depends on the theory that the mercury which is administered does not circulate in the blood as an albuminate, but as a double salt with excess of chloride of sodium. According to Stern we should use 0·008 to 0·010 gramme ($\frac{1}{8}$ to $\frac{1}{6}$ grain) of corrosive sublimate with ten times as much chloride of sodium dissolved in 2 c.cm. (30 mins.) of water as a dose;

such a solution is very much less irritating than that of the sublimate alone. On the other hand Bamberger recommends a solution (which had already been administered internally by Baerensprung) of albuminate of mercury in chloride of sodium. In order to make a soluble albuminate of mercury, diluted and filtered egg albumen was precipitated by the addition of corrosive sublimate, the precipitate dissolved in chloride of sodium, and the somewhat turbid solution filtered after standing a few days. In order to obtain a fluid which will contain 0·01 gramme ($\frac{1}{6}$ grain) of albuminate of mercury in 1 c.cm. (15 mins.) of solution, 100 parts of a solution of egg albumen (prepared by dissolving the albumen in $1\frac{1}{2}$ time its volume of distilled water), 60 parts of a 5 per cent. solution of corrosive sublimate, the same quantity of a 20 per cent. solution of common salt, and 80 parts of distilled water, are to be mixed together. This solution ought, if properly prepared and filtered, not to be more irritating than a solution of morphine. The complicated and difficult method of preparation will always, however, present a difficulty in the way of its more general use. Lately solutions of peptonate of mercury, as suggested by Paulcke, of Leipzig, and Friedländer, of Berlin, have come into use, which are made in the same way as the albuminate; according to some experiments which I have made, these fluids appear to be scarcely less irritating than solutions of corrosive sublimate, although they are to be preferred on account of their superior stability.

Among other preparations of mercury, *calomel* (Scarenzio and others), the *protiodide* (Bricheteau), the *biniodide* (Lewin), and lately the *cyanide* (Siegmund[1]) have been used by different physicians. None of these preparations possesses any therapeutic advantage over corrosive sublimate, to which they are inferior for subcutaneous use on account of their difficulty of solution. The cyanide is less insoluble than the others, and it has been injected by Siegmund in a dose of 0·7 c.cm. (10 mins.) of a solution containing 0·3 gramme (4 grains) to 35 c.cm. (1 ounce) of water = 0·006 gramme ($\frac{1}{10}$ grain) of the salt; the pain and

[1] *Wiener med. Wochenschrift*, 1876, No. 37. Vide also Güntz, *Wiener med. Presse*, 1880, No. 12.

local reaction are said to have been very slight, and mercury was found in the urine after two injections.

[More recently, Liebreich, the eminent pharmacologist of Berlin, has recommended the *formamide* of mercury (made by dissolving freshly precipitated peroxide of mercury in formamide) in preference to all other mercurial preparations for subcutaneous injection. It causes no pain or irritation, and is not precipitated by contact with the alkaline juices of the subcutaneous tissue.—TRANSL.]

ADDITIONAL NOTE ON SOME NEW ANTI-PYRETICS (P. 94), BY THE TRANSLATOR.

WITHIN the last few years chemists and therapeutists have been especially busy in a search for effective antipyretic medicines. They have been stimulated to this by a study of the chemical relations of one of the most effective, but most expensive, of our older antipyretics, viz. quinine. It has been known for a considerable time that when quinine is distilled with caustic potash a volatile nitrile base, *quinoline* (C_9H_7N), is obtained. Donath was the first to investigate the physiological action of this body, and pointed out that in many respects it resembled quinine, being both antiseptic and antipyretic. Later investigations, as those of Nahmmacher and of Brieger, however, showed that whilst, curiously enough, it generally could in a dose of 10 grains considerably lower the temperature of healthy men and of animals, yet it had practically no effect in the fever of typhus, typhoid, pneumonia, phthisis, &c. Here the matter stood until shortly afterwards, in 1881, Skraup discovered that quinoline could be obtained by treating a mixture of nitro-benzol, aniline, and glycerine with strong sulphuric acid. The synthetical preparation of this derivative of a costly antipyretic having been made possible, it then became a question of great interest whether the quinoline could not be so altered in its composition as to have imparted to it the properties of quinine. The practical solution of this problem has been engaging the skilled attention of several German chemists—notably, Fischer, of Munich; as also Riemer-Schmied (who assisted Fischer) and Hoffmann and Königs, and, still more recently, Knorr. The result of their labours has been the production from quinoline of a large number of bodies, some of which

appear to possess in a remarkable degree the antipyretic action of quinine. It is needless to describe the chemical processes by which these substances were obtained. Suffice it to say that, from a comparison of the constitution of the quinine molecule with that of quinoline, it was believed that the aim might be attained by processes of hydration, oxidation, and substitution, one of the primary alcoholic radicals being substituted for one or more atoms of hydrogen. In this manner such bodies as oxy-hydro-methyl-quinoline ($C_9H_{10}NO.CH_3$) and the corresponding ethyl compound ($C_9H_{10}NO.C_2H_5$) have been prepared, and to both of these has the name of *kairine* been given by Fischer, the latter being generally distinguished as Kairine A (A=Aethyl, *Ger.*), although, on account of its being latterly the only one of the two which is used therapeutically, it is known simply as kairine. Fischer has also prepared eth-oxy-hydro-methyl-quinoline. The name *kairoline* is employed to designate the methyl- and ethyl-tetrahydro-quinoline which have been obtained by Hoffmann and Königs from quinoline by a process of reduction and substitution. During last year (1884) Knorr, working in a somewhat different direction, has prepared a number of derivatives of a hypothetical base, *quinizine* ($C_9H_{10}N_2$), a body which stands in close relation to quinoline. The most important therapeutically of these derivatives appears to be dimethyl-oxy-quinizine ($C_{26}H_{18}N_4O_2$), or *antipyrine*, which is produced when aceto-acetate of ethyl is allowed to act on phenyl-hydrazine.

The physiological and therapeutical action of these and several other compounds derived from or directly related to quinoline has been investigated, and it has been found that especially kairine and antipyrine possess remarkable anti-pyretic properties.

Hydrochlorate of kairine occurs in the form of white crystals, which are freely soluble in water, and have a bitter, saline, and somewhat aromatic taste. Filehne and many others, who have administered it in various febrile diseases, have found that it rarely fails to powerfully reduce the temperature. Its action is quickly produced—within an hour—but unfortunately it does not last much longer than three hours. The action can, however, be maintained by the repeated adminis-

tration of the drug at short intervals of half an hour or an hour. It is advisable to give it in a dose of 5 to 10 grains every hour until the temperature has been lowered to 100° F., and to resume its administration when the temperature begins again to rise. If given too continuously, or in too large doses, it may in some cases produce cyanosis and collapse. It not only lowers the temperature, but it at the same time diminishes the pulse rate. Its action is generally accompanied by copious sweating; the urine becomes of a greenish colour from the presence of decomposed products of the drug, and albumen is occasionally met with. Some physicians consider it to be preferable to quinine, in respect of its antipyretic action being accompanied by few disagreeable secondary effects, excepting in some cases a peculiar pain in the nose and the frontal sinuses, and more or less irritation of the stomach, which sometimes gives rise to vomiting. Nothnagel, on the other hand, considers that these secondary effects are generally so intense as to constitute a distinct objection to its employment.

Antipyrine appears to be a remedy of much greater value. It is a white, highly crystalline body, which is freely soluble in water and alcohol, not very bitter, and more pleasant to the taste than either kairine or quinine. Its physiological and therapeutical action was first studied by Filehne. Immediately on the publication of his results, physicians everywhere began to try antipyrine in the treatment of all varieties of fever, so that the literature is already unusually large. It is perhaps too early as yet to draw any definite conclusions from these hasty investigations; but there seems to be no doubt whatever that in antipyrine we have an antipyretic which is only second in importance to quinine, and indeed in some respects is preferable. Generally speaking, it appears to produce its action more rapidly than quinine, and quite as rapidly as kairine; but the effect lasts much longer than that of the latter, and is not attended by the disagreeable symptoms which form an objection to the use of kairine. The only untoward effects which have been remarked are occasional vomiting, and, in exceptional cases, a measles-like eruption of reddish spots, which is mainly confined to the trunk, and may continue for some days. The dose is not yet fixed. Some physicians give 15 to

30 grains every hour until the desired lowering of the temperature is produced ; three or four such repetitions generally suffice. Others prefer to administer one large dose of 60 to 75 grains. In every case the antipyrine must again be given when the temperature begins once more to rise. It does not seem advisable to give, as a rule, more than 60 or 80 grains during one day, although in certain cases, especially those of typhoid fever, much larger doses are well borne. It is generally administered as a powder, or dissolved in water. On account of its great solubility in water—2 parts of it dissolving in 1 part of hot water, and the solution remaining clear, without deposition of crystals for some time—its aqueous solution has been injected subcutaneously (Rank). When so injected, Rank states that it produces no disagreeable local or general effects. But this has not been the experience of every subsequent observer (Erb, Vulpius). In a few cases it has been injected into the rectum. Antipyrine appears to be of distinct service in nearly all varieties of fever, specific or otherwise, where the fever runs a continuous course. It has therefore been found to be very useful in typhoid fever ; indeed, in certain cases Professor Erb has observed it reduce the temperature when the energetic application of cold baths failed to make much impression, and where even quinine had little effect. The temperature falls to the normal, and the pulse rate becomes less frequent ; occasionally there is sweating. Von Noorden states that the sweating may be prevented by the administration of a small dose of atropine —1 mgrm. ($\frac{1}{60}$ grain) per day. All observers agree as to the marked effect of antipyrine in typhoid. It has been used also with good effect in scarlatina, and in the fever accompanying pleurisy, pneumonia, phthisis, and erysipelas ; though, according to Von Noorden, the effect is slowly produced, and is not very lasting in cases of pneumonia and erysipelas. Cahn employed it with good result, in the Strasburg clinic, in a case of double-sided pneumonia in a pregnant woman, where quinine was contraindicated on account of its action on the uterus. Alexander has tried it, in the Breslau clinic, in several cases of acute rheumatism, and found that in the majority of the cases it not only reduced the temperature, but allayed the swelling

and pain of the joint affection. It does not, however, appear to be preferable to salicylate of soda.

Antipyrine seems, from our as yet limited experience, to have little action in typhus fever (Bielschowsky, of Breslau), and practically no effect in cases of recurrent fever (Bielschowsky) and intermittent fever (P. Guttmann, of Berlin, and Tilmann, in Leyden's clinic). Its failure to check the course of intermittent fever shows that, although one of the best, if not the best, of synthetically prepared antipyretic alkaloids, yet it does not possess certain of the most valuable properties of quinine. There is therefore still room for further chemical research in the direction of discovering effective substitutes for quinine. The great success already achieved leads us to hope that we shall very soon completely attain this object.

It may be remarked that antipyrine does not, like kairine, colour the urine. It produces no visible change in the urine, nor does it appear in the form of paired glycuronic acid ; the proportion of inorganic to ether-sulphuric acid is not altered (Cahn).

It is interesting to note that most of the important antipyretics belong chemically to the so called aromatic group (derivatives of benzol), a group which at the same time yields many of our best antiseptics. Thus carbolic acid, salicylic acid, benzoic acid, kairine, antipyrine, quinine, and the other alkaloids of cinchona, are all of them members of this group. This fact tends to confirm a somewhat general belief that some, if not all, of our most efficient antipyretics owe their action to their antiseptic properties.

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END OF THE SECOND VOLUME.

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